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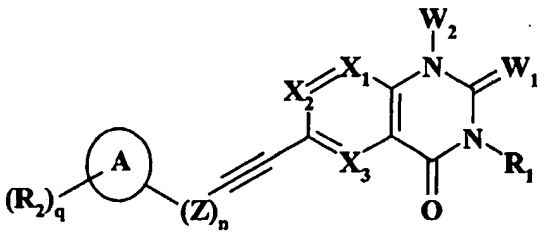
(54) Title: ALKYNLATED FUSED RING PYRIMIDINE COMPOUNDS AS MATRIX METALLOPROTEASE-13 INHIBITOR



(I)

(57) Abstract: A compound selected from those of formula (I) : wherein W_1 represents O, S, or $-NR_3$ in which R_3 represents hydrogen, alkyl, OH or CN; W_2 represents a group selected from hydrogen, CF_3, NH_2, monoalkylamino, dialkylamino, alkyl, alkenyl, alkynyl, aryl, arylalkyl, cycloalkylalkyl, heterocycle, these groups being optionally substituted, or W_1 and W_2 form together a group of formula $-N=X_4-W_3-$ as defined in the description, X_1, X_2 and X_3 represent N or C optionally substituted, n is 0 to 8, Z represents $-CR_{12}R_{13}$, wherein R_{12} and R_{13} are as defined in the description, A represents a ring system, the groups R_2 represent hydrogen, alkyl, halogen, cyano, nitro, trihalogenoalkyl, $-NR_{10}R_{11}$, $-OR_{14}$, $-SR_{14}$, $-SOR_{14}$, $-SO_2R_{14}$, acyl, $-(CH_2)_kNR_{10}R_{11}$, $-X_5(CH_2)_kNR_{10}R_{11}$, $-(CH_2)_kSO_2NR_{14}R_{15}$, $-X_5(CH_2)_kC(=O)OR_{14}$, $-(CH_2)_kC(=O)OR_{14}$, $-X_5(CH_2)_kC(=O)NR_{14}R_{15}$, $-(CH_2)_kC(=O)NR_{14}R_{15}$ and $-X_6-R_{16}$ in which X_5, k; R_{10}, R_{11}, R_{14} , R_{15}, X_6, and R_{16} are as defined in the description, q is 0 to 7; R_1 represents hydrogen, alkyl, alkenyl, alkynyl, or a ring system, and optionally, its optical isomers , N-oxide, and addition salts thereof with a pharmaceutically-acceptable acid or base, and medicinal products containing the same are useful as specific inhibitors of type-13 matrix mettaloprotease.

TITLE OF THE INVENTION

ALKYNLATED FUSED RING PYRIMIDINE COMPOUNDS AS MATRIX METALLOPROTEASE-13 INHIBITOR

FIELD OF THE INVENTION

The present invention relates to novel alkynylated fused ring pyrimidine compounds which are useful for preparing medicinal products for treating complaints involving a therapy with a matrix metalloprotease-13 (MMP-13) inhibitor. These medicinal products are useful in particular for treating certain inflammatory conditions such as rheumatoid arthritis or osteoarthritis, as well as certain proliferative conditions such as cancers.

TECHNOLOGICAL BACKGROUND OF THE INVENTION

Matrix metalloproteases (MMPs) are enzymes which are involved in the renewal of extracellular matrix tissue, such as cartilage, tendons and joints. MMPs bring about the destruction of the extracellular matrix tissue, which is compensated for, in a non-pathological physiological state, by its simultaneous regeneration.

Under normal physiological conditions, the activity of these extremely aggressive peptidases is controlled by specialized proteins which inhibit MMPs, such as the tissue inhibitors of metalloprotease (TIMPs).

Local equilibrium of the activities of MMPs and of TIMPs is critical for the renewal of the extracellular matrix. Modifications of this equilibrium which result in an excess of active MMPs, relative to their inhibitor, induce a pathological destruction of cartilage, which is observed in particular in rheumatoid arthritis and in osteoarthritis.

In pathological situations, an irreversible degradation of articular cartilage takes place, as is the case in rheumatic diseases such as rheumatoid arthritis or osteoarthritis. In these pathologies, the cartilage degradation process predominates, leading to a destruction of the tissue and resulting in a loss of function.

At least twenty different matrix metalloproteases have been identified to date and are subdivided into four groups, the collagenases, the gelatinases, the stromelysins and the membrane-type MMPs (MT-MMPs), respectively.

Matrix metalloprotease-13 (MMP-13) is a collagenase-type MMP which constitutes the predominant collagenase observed during osteoarthritis, in the course of which pathology the chondrocyte directs the destruction of cartilage.

There is a need in the prior art for novel MMP inhibitors, more particularly for MMP-13 inhibitors, in order to prevent and/or correct the imbalance in the renewal of extracellular matrix tissue, such as arthritis, rheumatoid arthritis, osteoarthritis, osteoporosis, periodontal diseases, inflammatory bowel disease, psoriasis, multiple sclerosis, cardiac insufficiency, atherosclerosis, asthma, chronic obstructive pulmonary diseases (COPD), age-related macular degeneration (ARMD) and cancer.

MMP-inhibitor compounds are known. Most of these MMP-inhibitors are not selective for a single MMP, such as those described by Montana and Baxter (2000) or by Clark et al. (2000).

There is also a need in the prior art for novel inhibitors that are active on matrix metalloprotease-13, in order to enrich the therapeutic arsenal that can be used for treating pathologies associated with the destruction of the extracellular matrix and with cancer.

PRIOR ART DESCRIPTION

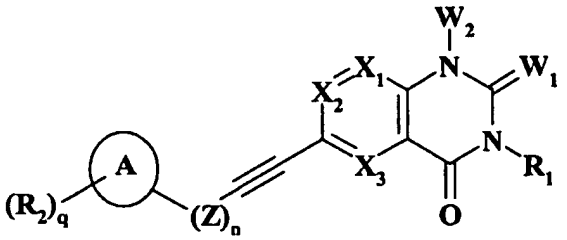
The patent application WO9826664 describes quinazolinone compounds which are used as new antifungic compounds. The US patent 5,389,631 describes new dioxoquinazoline and dioxobenzodiazepine amino acid derivatives which are analogs as fibrinogen receptor antagonists and can be used in the treatment of pathologies wherein inhibition of the fibrinogen of blood and inhibition of the aggregation of blood platelets are involved.

The compounds of the present application are novel and represent powerful inhibitors of MMP-13. They are consequently of use in the treatment of rheumatoid arthritis, osteoarthritis, osteoporosis, periodontal diseases, inflammatory bowel disease, psoriasis, multiple sclerosis, cardiac insufficiency, atherosclerosis, asthma, chronic obstructive pulmonary diseases (COPDs), age-related degeneration (ARMD) and cancer.

SUMMARY OF THE INVENTION

The applicant has identified novel alkynylated fused ring pyrimidine compounds that are matrix metalloprotease inhibitors, and more specifically compounds that are selective MMP-13 inhibitors.

More specifically, the present invention relates to compounds of formula (I) :



(I)

wherein

W_1 represents an oxygen atom, a sulfur atom, or a $-NR_3$ group in which R_3 represents hydrogen atom, (C_1-C_6)alkyl, hydroxyl or cyano,

W_2 represents a group selected from :

- hydrogen atom, trifluoromethyl, amino, mono(C_1-C_{10})alkylamino, di(C_1-C_{10})alkylamino, each alkyl moiety being identical or different,
- (C_1-C_6)alkyl, (C_3-C_6)alkenyl, (C_3-C_6)alkynyl, (C_5-C_{10})aryl, (C_5-C_{10})aryl(C_1-C_{10})alkyl, (C_3-C_{10})cycloalkyl(C_1-C_{10})alkyl, and the residue of an aromatic or non aromatic heterocycle comprising 5 or 6 ring members including from 1 to 4 hetero atoms selected from nitrogen, oxygen and sulfur, these groups being optionally substituted by one or more groups, which may be identical or different, selected from halogen, amino, mono(C_1-C_{10})alkylamino, di(C_1-C_{10})alkylamino, each alkyl moiety being identical or different, cyano, trihalogeno(C_1-C_6)alkyl, (C_1-C_6)acyl, $-C(=O)OR_4$, $-OR_4$ and $-SR_4$, R_4 representing a hydrogen atom or a (C_1-C_6)alkyl group,

or **W_1 and W_2** form together a group of formula $N-X_4=W_3$ (in which the nitrogen atom is bonded on the place of the group W_1 and the group W_3 is bonded on the place of the group W_2) wherein:

- W_3 represents a nitrogen atom or a group $-CR_5$ in which R_5 is selected from :
  - a hydrogen atom,
  - $-OR_6$, $-SR_6$ in which R_6 is selected from hydrogen, (C_1-C_6)alkyl and (C_5-C_{10})aryl(C_1-C_{10})alkyl;
  - (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, the residue of a saturated heterocycle comprising from 3 to 8 ring members including one hetero atom selected from oxygen, sulfur and nitrogen, (C_5-C_{10})aryl, (C_5-C_{10})heteroaryl comprising from 1 to 4 hetero atoms selected from oxygen, sulfur and nitrogen, and (C_5-C_{10})aryl(C_1-C_{10})alkyl, these groups being optionally substituted by $-(CH_2)_p-OH$ or $-(CH_2)_p-NH_2$, wherein p is an integer from 0 to 4 inclusive,
- X_4 represents a nitrogen atom or a group $-CR_7$ in which R_7 is selected from hydrogen, $-NR_8R_9$, $-OR_8$, $-SR_8$, (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, the residue of a saturated heterocycle comprising from 3 to 8 ring members including one hetero atom selected from oxygen, sulfur and nitrogen, (C_5-C_{10})aryl, (C_5-C_{10})heteroaryl comprising from 1 to 4 hetero atoms selected from oxygen, sulfur and nitrogen, and (C_5-C_{10})aryl(C_1-C_{10})alkyl, these groups being optionally substituted by $-(CH_2)_p-OH$ or $-(CH_2)_p-NH_2$, wherein p is an integer from 0 to 4 inclusive,
  and in which R_8 and R_9, identical or different, are selected from hydrogen, (C_1-C_6)alkyl and (C_5-C_{10})aryl(C_1-C_{10})alkyl,

X_1, X_2 and **X_3** represent, independently of each other, a nitrogen atom or a carbon atom, the said carbon atom being unsubstituted or substituted with a group selected from :

- (C_1-C_6)alkyl, hydroxyl, (C_1-C_6)alkoxy, halogen, trifluoromethyl, cyano, nitro,
- $-S(O)_{n1}R_4$ wherein n_1 represents an integer from 0 to 2 inclusive and R_4 represents an hydrogen atom or a (C_1-C_6)alkyl group,
- and $-NR_{10}R_{11}$ wherein R_{10} and R_{11}, which may be identical or different, represent a group selected from hydrogen atom, (C_1-C_6)alkyl, and (C_5-C_{10})aryl(C_1-C_{10})alkyl, or R_{10} and R_{11} form together with the nitrogen atom to which there are bonded, a 5- or 6-ring members which can optionally contain a second hetero atom selected from nitrogen and oxygen,

with the proviso that not more than two of the groups X_1, X_2 and X_3 simultaneously represent a nitrogen atom,

n is an integer from 0 to 8 inclusive,

Z represents $-CR_{12}R_{13}$, wherein R_{12} and R_{13} independently of each other, represent a group selected from hydrogen, (C_1-C_6)alkyl, trihalogeno(C_1-C_6)alkyl, halogen, amino, mono(C_1-C_6)alkylamino, di(C_1-C_6)alkylamino in which each alkyl moiety is identical or different, $-OR_4$, $-SR_4$, and $-C(=O)OR_4$, R_4 being as defined hereinbefore, or $-CR_{12}R_{13}$ form together a carbonyl group, and

-when n is greater than or equal to 2, the hydrocarbon chain Z optionally contains one or more multiple bonds,

-and/or one of the carbon atoms in the hydrocarbon chain Z may be replaced with an oxygen atom, a sulfur atom which is unsubstituted or substituted with one or two oxygen, or a nitrogen atom which is unsubstituted or substituted with a (C_1-C_6)alkyl,

A represents the residue of an aromatic or non-aromatic 5- or 6-membered monocycle comprising from 0 to 4 hetero atoms selected from nitrogen, oxygen and sulfur, or a bicycle composed of two aromatic or non-aromatic 5- or 6-membered rings, which may be identical or different, comprising from 0 to 4 hetero atoms selected from nitrogen, oxygen and sulfur,

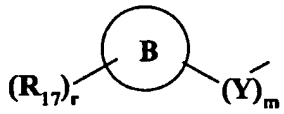
the groups R_2, which may be identical or different, are selected from hydrogen, (C_1-C_6)alkyl, halogen, cyano, nitro, trihalogeno(C_1-C_6)alkyl, $-NR_{10}R_{11}$, $-OR_{14}$, $-SR_{14}$, $-SOR_{14}$, $-SO_2R_{14}$, (C_1-C_6)acyl, $-(CH_2)_kNR_{10}R_{11}$, $-X_5(CH_2)_kNR_{10}R_{11}$, $-(CH_2)_kSO_2NR_{14}R_{15}$, $-X_5(CH_2)_kC(=O)OR_{14}$, $-(CH_2)_kC(=O)OR_{14}$, $-X_5(CH_2)_kC(=O)NR_{14}R_{15}$, $-(CH_2)_kC(=O)NR_{14}R_{15}$ and $-X_6-R_{16}$ in which :

- X_5 represents an oxygen atom, a sulfur atom, a -NH group, or a $-N(C_1-C_6)$alkyl group,
- k is an integer from 0 and 3 inclusive,
- R_{10} and R_{11} are as defined hereinbefore,
- R_{14} and R_{15}, identical or different, represent hydrogen or (C_1-C_6)alkyl,
- X_6 represents a single bond, $-CH_2-$, an oxygen atom or a sulfur atom which is unsubstituted or substituted with one or two oxygen atoms,

- R_{16} represents the residue of an aromatic or non-aromatic, heterocyclic or non-heterocyclic, 5- or 6-membered ring which is unsubstituted or substituted with one or more groups, which may be identical or different, selected from (C_1-C_6)alkyl, halogen, trihalogeno(C_1-C_6)alkyl, hydroxyl, (C_1-C_6)alkoxy, mercapto, (C_1-C_6)alkylthio, amino, mono(C_1-C_6)alkylamino, di(C_1-C_6)alkylamino each alkyl moiety being identical or different, and when the ring is heterocyclic, it comprises from 1 to 4 hetero atoms selected from nitrogen, oxygen and sulfur,

q is an integer from 0 to 7 inclusive,

$\mathbf{R_1}$ represents a group selected from hydrogen, (C_1-C_6)alkyl, (C_3-C_6)alkenyl, and (C_3-C_6)alkynyl, the groups alkyl, alkenyl and alkynyl being optionally substituted with one or more groups, which may be identical or different, selected from amino, mono(C_1-C_6)alkylamino, di(C_1-C_6)alkylamino in which each alkyl moiety is identical or different, (C_1-C_6)alkyl, cyano, trihalogeno(C_1-C_6)alkyl, $-C(=O)OR_4$, $-OR_4$, $-SR_4$, in which R_4 is as defined above, and the group of formula :



in which:

- m is an integer from 0 to 8 inclusive,
- Y represents $-CR_{18}R_{19}$, wherein R_{18} and R_{19} independently of each other, represent a group selected from hydrogen, (C_1-C_6)alkyl, phenyl, trihalogeno(C_1-C_6)alkyl, halogen, amino, mono(C_1-C_6)alkylamino, di(C_1-C_6)alkylamino in which each alkyl moiety is identical or different, $-OR_4$, $-SR_4$ or $-C(=O)OR_4$ wherein R_4 is as defined above, and
  - when m is greater than or equal to 2, the hydrocarbon chain Y optionally contains one or more multiple bonds,
  - and/or one of the carbon atoms in the hydrocarbon chain Y may be replaced with an oxygen atom, a sulfur atom which is unsubstituted or substituted with one or two oxygen, or a nitrogen atom which is unsubstituted or substituted with (C_1-C_6)alkyl,
- B represents a group selected from the residue of an aromatic or non-aromatic, 5- or 6-membered monocycle comprising from 0 to 4 hetero atoms selected from nitrogen,

oxygen and sulfur, and a bicycle, composed of two aromatic or non-aromatic, 5- or 6-membered rings, which may be identical or different, comprising from 0 to 4 hetero atoms selected from nitrogen, oxygen and sulfur,

- r is an integer from 0 to 7 inclusive,
- the group(s) R_{17} which may be identical or different are selected from hydrogen, (C_1-C_6)alkyl, halogen, cyano, nitro, trihalogeno(C_1-C_6)alkyl, $-NR_{10}R_{11}$, $-OR_{14}$, $-SR_{14}$, $-SOR_{14}$, $-SO_2R_{14}$, (C_1-C_6)acyl, $-(CH_2)_kNR_{10}R_{11}$, $-X_5(CH_2)_kNR_{10}R_{11}$, $-(CH_2)_kSO_2NR_{14}R_{15}$, $-X_5(CH_2)_kC(=O)OR_{14}$, $-(CH_2)_kC(=O)OR_{14}$, $-X_5(CH_2)_kC(=O)NR_{14}R_{15}$, $-(CH_2)_kC(=O)NR_{14}R_{15}$ and the group of formula $-X_6-R_{16}$ in which X_5, k, R_{10}, R_{11}, R_{14}, R_{15}, X_6 and R_{16} are as defined hereinbefore, and

optionally, their optical isomers , N-oxides, and addition salts thereof with a pharmaceutically-acceptable acid or base.

According to a first embodiment, the invention relates to compounds of formula (I) wherein :

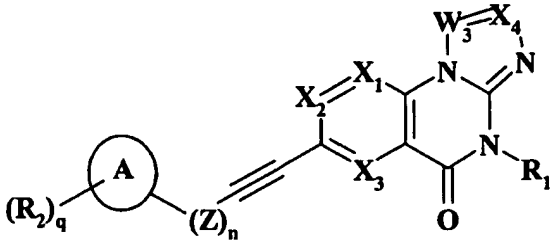
W_1 represents an oxygen atom, a sulfur atom, or a $-NR_3$ group in which R_3 represents hydrogen atom, (C_1-C_6)alkyl, hydroxyl or cyano,

W_2 represents a group selected from :

- hydrogen atom, trifluoromethyl, amino, mono(C_1-C_{10})alkylamino, di(C_1-C_{10})alkylamino, each alkyl moiety being identical or different,
- (C_1-C_6)alkyl, (C_3-C_6)alkenyl, (C_3-C_6)alkynyl, (C_5-C_{10})aryl, (C_5-C_{10})aryl(C_1-C_{10})alkyl, (C_3-C_{10})cycloalkyl(C_1-C_{10})alkyl, and the residue of an aromatic or non aromatic heterocycle comprising 5 or 6 ring members including from 1 to 4 hetero atoms selected from nitrogen, oxygen and sulfur, these groups being optionally substituted by one or more groups, which may be identical or different, selected from halogen, amino, mono(C_1-C_{10})alkylamino, di(C_1-C_{10})alkylamino, each alkyl moiety being identical or different, cyano, trihalogeno(C_1-C_6)alkyl, (C_1-C_6)acyl, $-C(=O)OR_4$, $-OR_4$ and $-SR_4$, R_4 representing a hydrogen atom or a (C_1-C_6)alkyl group,

and X_1, X_2, X_3, R_1, R_2, A, Z, n and q are as defined hereinbefore.

According to a second embodiment, the invention relates to compounds of formula (I) corresponding to formula (IA) :



(I/A)

wherein :

W_3 represents a nitrogen atom or a group $-CR_5$ in which R_5 is selected from :

- a hydrogen atom,
- $-OR_6$, $-SR_6$ in which R_6 is selected from hydrogen, (C_1-C_6)alkyl and (C_5-C_{10})aryl(C_1-C_{10})alkyl;
- (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, the residue of a saturated heterocycle comprising from 3 to 8 ring members including one hetero atom selected from oxygen, sulfur and nitrogen, (C_5-C_{10})aryl, (C_5-C_{10})heteroaryl comprising from 1 to 4 hetero atoms selected from oxygen, sulfur and nitrogen, and (C_5-C_{10})aryl(C_1-C_{10})alkyl, these groups being optionally substituted by $-(CH_2)_p-OH$ or $-(CH_2)_p-NH_2$, wherein p is an integer from 0 to 4 inclusive,

X_4 represents a nitrogen atom or a group $-CR_7$ in which R_7 is selected from hydrogen, $-NR_8R_9$, $-OR_8$, $-SR_8$, (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, the residue of a saturated heterocycle comprising from 3 to 8 ring members including one hetero atom selected from oxygen, sulfur and nitrogen, (C_5-C_{10})aryl, (C_5-C_{10})heteroaryl comprising from 1 to 4 hetero atoms selected from oxygen, sulfur and nitrogen, and (C_5-C_{10})aryl(C_1-C_{10})alkyl, these groups being optionally substituted by $-(CH_2)_p-OH$ or $-(CH_2)_p-NH_2$, wherein p is an integer from 0 to 4 inclusive,

and in which R_8 and R_9, identical or different, are selected from hydrogen, (C_1-C_6)alkyl and (C_5-C_{10})aryl(C_1-C_{10})alkyl,

and X_1, X_2, X_3, R_1, R_2, A, Z, n and q are as defined in formula (I).

The invention relates particularly to the compounds of formula (I) in which:

W_2 represents a group selected from hydrogen atom, $(C_1\text{-}C_6)$alkyl, $(C_5\text{-}C_8)$aryl$(C_1\text{-}C_6)$alkyl and $(C_3\text{-}C_6)$cycloalkyl$(C_1\text{-}C_6)$alkyl,

W_1 represents an oxygen atom or a sulfur atom,

X_1 represents a -CH group,

X_2 represents a -CH group or a nitrogen atom,

X_3 represents a -CH group,

and R_1, R_2, A, Z, n and q are as defined in formula (I).

The invention also relates to the compounds of general formula (I) in which:

W_2 represents a group selected from hydrogen atom, amino, mono$(C_1\text{-}C_{10})$alkylamino, di$(C_1\text{-}C_{10})$alkylamino each alkyl moiety being identical or different, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$alkenyl, $(C_3\text{-}C_6)$alkynyl, $(C_5\text{-}C_{10})$aryl, $(C_5\text{-}C_{10})$aryl$(C_1\text{-}C_6)$alkyl, and $(C_3\text{-}C_6)$cycloalkyl$(C_1\text{-}C_6)$alkyl,

W_1 represents an oxygen atom or a sulfur atom,

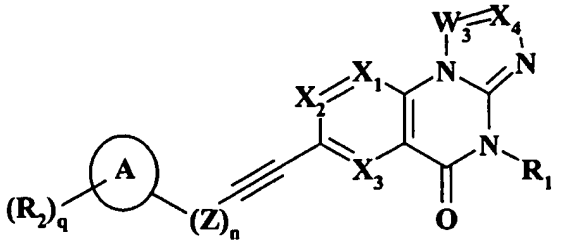
X_1 represents a nitrogen atom or a –CH group

X_2 represents a -CH group,

X_3 represents a -CH group,

and R_1, R_2, A, Z, n and q are as defined in formula (I).

The invention relates particularly to the compounds of formula (IA) :



(I/A)

wherein :

W_3 represents $-CR_5$ wherein R_5 represents a hydrogen atom or a methyl group,

X_4 represents a nitrogen atom or $-CR_7$ wherein R_7 represents a hydrogen atom or a methyl group,

n is an integer from 1 to 4 inclusive,

and X_1, X_2, X_3, R_1, R_2, A, Z and q are as defined in the formula (I).

The invention also relates to the compounds of formula (I) in which:

A represents a group selected from phenyl, pyridyl, thienyl, imidazolyl, furyl, benzodioxolyl, benzodioxinyl, benzothienyl, benzofuryl, benzo-1,2,5-thiadiazolyl, benzo-1,2,5-oxadiazolyl and indolyl,

q is an integer from 0 to 4 inclusive,

the group(s) R_2, which may be identical or different, are selected from hydrogen, (C_1-C_6)alkyl, halogen, cyano, nitro, trihalogeno(C_1-C_6)alkyl, $-NR_{14}R_{15}$, $-OR_{14}$, $-SO_2R_{14}$, $-(CH_2)_kSO_2NR_{14}R_{15}$, $-X_5(CH_2)_kC(=O)OR_{14}$, $-(CH_2)_kC(=O)OR_{14}$, $-X_5(CH_2)_kC(=O)NR_{14}R_{15}$, $-(CH_2)_kC(=O)NR_{14}R_{15}$ and $-X_6-R_{16}$ in which :

- X_5 represents an oxygen atom, a sulfur atom, or a -NH group,
- k is an integer from 0 and 3 inclusive,
- R_{14} and R_{15} identical or different represent hydrogen or (C_1-C_6)alkyl,
- X_6 represents an oxygen atom,
- R_{16} represents a phenyl group which is unsubstituted or substituted with one or more groups, which may be identical or different, selected from (C_1-C_6)alkyl, halogen, and hydroxyl,

and W_1, W_2, X_1, X_2, X_3, R_1, Z and n are as defined in formula (I).

The invention also relates to the compounds of formula (I) in which:

A represents a group selected from phenyl, pyridinyl, thienyl, imidazolyl, furyl, and benzodioxolyl,

q is an integer from 0 to 4 inclusive,

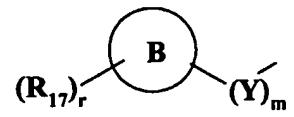
the group(s) R_2, which may be identical or different, are selected from hydrogen, (C_1-C_6)alkyl, halogen, cyano, nitro, trihalogeno(C_1-C_6)alkyl, $-NR_{14}R_{15}$, $-OR_{14}$, $-SO_2R_{14}$, $-(CH_2)_kSO_2NR_{14}R_{15}$, $-X_5(CH_2)_kC(=O)OR_{14}$, $-(CH_2)_kC(=O)OR_{14}$, $-X_5(CH_2)_kC(=O)NR_{14}R_{15}$, and $-(CH_2)_kC(=O)NR_{14}R_{15}$ in which :

- X_5 represents an oxygen atom, a sulfur atom, or a -NH group,
- k is an integer from 0 and 3 inclusive,

- R_{14} and R_{15} identical or different represent hydrogen or $(C_1$-$C_6)$alkyl,

and W_1, W_2, X_1, X_2, X_3, R_1, Z and n are as defined in formula (I).

The invention also relates to the compounds of formula (I) in which $\mathbf{R_1}$ represents hydrogen, $(C_1$-$C_6)$alkyl or the group of formula :

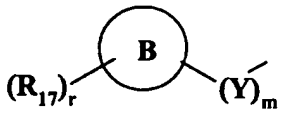


in which:

- m is an integer from 0 to 3 inclusive,
- Y represents $-CR_{18}R_{19}$, wherein R_{18} and R_{19} independently of each other, represent a group selected from hydrogen, $(C_1$-$C_6)$alkyl, and phenyl,
  - and when m is greater than or equal to 2, the hydrocarbon chain Y optionally contains one multiple bonds,
  - and/or one of the carbon atoms in the hydrocarbon chain Y may be replaced with an oxygen atom, a sulfur atom which is unsubstituted or substituted with one or two oxygen, or a nitrogen atom which is unsubstituted,
- B represents a group selected from phenyl, pyridinyl, thienyl, imidazolyl, furyl, benzodioxolyl, benzodioxinyl, benzothienyl, benzofuryl, benzo-1,2,5-thiadiazolyl, benzo-1,2,5-oxadiazolyl, naphtyl and indolyl,
- r is an integer from 0 to 3 inclusive,
- the group(s) R_{17} which may be identical or different are selected from hydrogen, $(C_1$-$C_6)$alkyl, halogen, cyano, nitro, trihalogeno$(C_1$-$C_6)$alkyl, $-NR_{14}R_{15}$, $-OR_{14}$, $-SO_2R_{14}$, $(CH_2)_kSO_2NR_{14}R_{15}$, $X_5(CH_2)_kC(=O)OR_{14}$, $(CH_2)_kC(=O)OR_{14}$, $X_5(CH_2)_kC(=O)NR_{14}R_{15}$, $-(CH_2)_kC(=O)NR_{14}R_{15}$ wherein :
  - k is an integer from 0 to 3 inclusive,
  - X_5 represents an oxygen atom, a sulfur atom, or a group –NH,
  - R_{14} and R_{15}, identical or different, represent a hydrogen atom or a $(C_1$-$C_6)$alkyl group,

and W_1, W_2, X_1, X_2, X_3, R_2, Z, n and q are as defined in formula (I).

The invention relates also to the compound of formula (I) in which R_1 represents a group of formula :



in which:

- m is an integer from 0 to 3 inclusive,
- Y represents $-CR_{18}R_{19}$, wherein R_{18} and R_{19} independently of each other, represent a group selected from hydrogen and methyl,
  - and when m is greater than or equal to 2, the hydrocarbon chain Y optionally contains one double bonds,
  - and/or one of the carbon atoms in the hydrocarbon chain Y may be replaced with an oxygen atom, a sulfur atom which is unsubstituted or substituted with one or two oxygen, or a nitrogen atom which is unsubstituted,
- B represents a group selected from phenyl, pyridinyl, thienyl, imidazolyl, furyl, and benzodioxolyl,
- r is an integer from 0 to 3 inclusive,
- the group(s) R_{17} which may be identical or different are selected from hydrogen, $(C_1\text{-}C_6)$alkyl, halogen, cyano, nitro, trihalogeno$(C_1\text{-}C_6)$alkyl, $-NR_{14}R_{15}$, $-OR_{14}$, $-SO_2R_{14}$, $(CH_2)_kSO_2NR_{14}R_{15}$, $X_5(CH_2)_kC(=O)OR_{14}$, $(CH_2)_kC(=O)OR_{14}$, $X_5(CH_2)_kC(=O)NR_{14}R_{15}$, $-(CH_2)_kC(=O)NR_{14}R_{15}$ wherein :
  - k is an integer from 0 to 3inclusive,
  - X_5 represents an oxygen atom, a sulfur atom, or a group -NH,
  - R_{14} and R_{15}, identical or different, represent a hydrogen atom or a $(C_1\text{-}C_6)$alkyl group,

and W_1, W_2, X_1, X_2, X_3, R_2, Z, n and q are as defined in formula (I).

Preferred compounds of the invention are those compounds of formula (I) wherein n is equal to one.

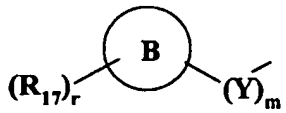
Advantageously, preferred compounds of the invention are those compounds of formula (I) wherein Z represents a group $-CR_{12}R_{13}$ in which R_{12} and R_{13} represent each a hydrogen atom.

Another preferred compounds of the invention are compounds of formula (I) wherein A represents a 5- to 6- membered aromatic monocycle optionally substituted by one or more groups R_2 as defined in the compound of formula (I).

The substituent A that is preferred according to the invention is the phenyl group optionally substituted by one group R_2 as defined in the compound of the formula (I).

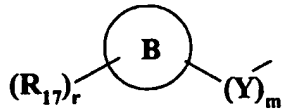
Especially preferred compounds of the invention are compounds of formula (I) wherein A represents a phenyl group and R_2 represents a methoxy group.

Still other preferred compounds of the invention are compounds of formula (I) wherein W_2 represents an oxygen atom, W_1 represents a linear or branched (C_1-C_6)alkyl group and R_1 represents a group of formula :



in which Y, B, R_{17}, m and r are as defined in the compound of formula (I).

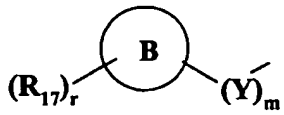
The substituent R_1 that is preferred according to the invention is the group of formula :



in which m is equal to one, Y represents a methylene group, B represents a phenyl group which is optionally substituted with one group R_{17} which represents a group $(CH_2)_k-C(=O)OR_{14}$ in which k and R_{14} are as defined in the compound of formula (I).

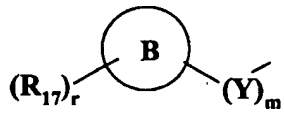
Still other preferred compounds of the invention are compounds of formula (IA) wherein W_1 and W_2 form together a group or formula $N-X_4=W_3$ wherein W_3 represents a group -

CR_5 in which R_5 is an hydrogen atom, X_4 represents an nitrogen atom and R_1 represents a group of formula :



in which Y, B, R_{17}, m and r are as defined in the compound of formula (IA).

Still other preferred compounds of the invention are compounds of formula (IA) wherein R_1 represents a group of formula :



in which m is equal to one, Y represents a methylene group, B represents a phenyl group which is optionally substituted with one group R_{17} which represents a group $-(CH_2)_k-C(=O)OR_{14}$ in which k and R_{14} are as defined in the compound of formula (IA).

More particularly, the invention related to the following compounds of formula (I) :

Methyl 4-{6-[3-(4-methoxyphenyl)-prop-1-ynyl]-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl}-benzoate,

4-[1-Methyl-2,4-dioxo-6-(3-phenyl-prop-1-ynyl)-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoic acid,

4-{6-[3-(4-Methoxy-phenyl)-prop-1-ynyl]-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl}-benzoic acid,

4-[1-Methyl-2,4-dioxo-6-(3-phenyl-prop-1-ynyl)-1,4-dihydro-2*H*-pyrido[3,4-*d*]pyrimidin-3-ylmethyl]-benzoic acid,

4-{6-[3-(4-Methoxy-phenyl)-prop-1-ynyl]-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-pyrido[3,4-*d*]pyrimidin-3-ylmethyl}-benzoic acid,

4-Benzyl-7-(3-phenyl-prop-1-ynyl)-4*H*-[1,2,4]triazolo[4,3-*a*]quinazolin-5-one,

4-Benzyl-7-[(4-methoxyphenyl)-prop-1-ynyl]-4*H*-[1,2,4]-triazolo[4,3-*a*] quinazolin-5-one,

Methyl 4-{7-[3-(4-methoxy-phenyl)-prop-1-ynyl]-5-oxo-5*H*-[1,2,4]triazolo[4,3-*a*] quinazolin-4-ylmethyl}-benzoate,

4-[5-Oxo-7-(3-phenyl-prop-1-ynyl)-5*H*-[1,2,4]triazolo[4,3-*a*]quinazolin-4-ylmethyl]-benzoic acid,

and 4-(1-Methyl-2,4-dioxo-6-(2-phenylethynyl)-1,4-dihydro-2H-quinazolin-3-ylmethyl)-benzoic acid.

The optical isomers, the N-oxides, as well as the addition salts with a pharmaceutically-acceptable acid or base, of the preferred compounds form an integral part of the invention.

The invention also relates to a pharmaceutical composition comprising as active ingredient an effective amount of a compound of formula (I) together with one or more pharmaceutically-acceptable excipients or carriers.

Another embodiment of the invention concerns the use of the compound of formula (I) for the preparation of a medicinal product intended for treating a disease involving therapy by inhibition of matrix metalloprotease, and more particularly of type-13 matrix metalloprotease.

The invention also relates to a method for treating a living body afflicted with a disease involving a therapy by inhibition of matrix metalloprotease, and more particularly of type-13 matrix metalloprotease, the said method comprising the administration of an effective amount of a compound of formula (I) to a patient in need thereof.

A preferred method of treatment according to this invention is treatment of a disease selected from arthritis, rheumatoid arthritis, osteoarthritis, osteoporosis, periodontal diseases, inflammatory bowel disease, psoriasis, multiple sclerosis, cardiac insufficiency, atherosclerosis, asthma, chronic obstructive pulmonary diseases, age-related degeneration and cancers.

DETAILED DESCRIPTION OF THE INVENTION

The compounds provided by this invention are those defined in formula (I). In formula (I), it is understood that :

- a (C_1-C_6)alkyl group and a (C_1-C_{10})alkyl group denote a linear or branched group containing respectively from 1 to 6 or from 1 to 10 carbon atoms ; example of such groups,

without implying any limitation are methyl, ethyl, propyl, isopropyl, tert-butyl, neopentyl, hexyl, heptyl, 3-methyl-hexyl, ...

- a (C_3-C_6)alkenyl group denotes a linear or branched group containing from 3 to 6 carbon atoms, and one or more double bonds ; examples of such groups without implying any limitation are allyl, 3-buten-1-yl, 2-methyl-buten-1-yl, hexenyl, ...

- a (C_3-C_6)alkynyl group denotes a linear or branched group containing from 3 to 6 carbon atoms, and one or more triple bonds ; examples of such groups without implying any limitation are 3-butyn-1-yl, 2-methyl-butyn-1-yl, hexynyl, ...

- a (C_1-C_6)alkoxy group means the alkyl group as mentioned above bound through an oxygen atom ; examples of such compounds without implying any limitation are metoxy, ethoxy, *n*-propyloxy, *tert*-butyloxy, ...

- a (C_1-C_6)alkylamino or (C_1-C_{10})alkylamino means the alkyl groups as defined above bound through a nitrogen atom ; example of such groups, without implying any limitation are methyl amino, isobutyl amino, dimethylamino, ethylamino, diethylamino, ...

- a (C_5-C_{10})aryl group denotes an aromatic system containing from 5 to 8 carbon atoms ; examples of such groups without implying any limitation are cyclopentadienyl, phenyl, naphthyl, indenyl,...

- a (C_5-C_{10})heteroaryl group denotes an aromatic system as described above in which 1 to 4 carbon atoms are replaced by 1 to 4 hetero atoms selected from oxygen, sulfur and nitrogen ; examples of such groups without implying any limitation are furyl, thienyl, pyrrolyl, pyrazolyl, pyridyl, pyrimidyl, pyrazinyl, benzofuryl, benzothienyl, indolyl, quinolyl, isoquinolyl, benzodioxolyl, benzodioxinyl, benzo[1,2,5]thiadiazolyl, benzo[1,2,5]oxadiazolyl,...

- a (C_3-C_{10})cycloalkyl group denotes a cyclic system containing from 3 to 10 carbon atoms ; examples of such groups without implying any limitation are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclooctyl, cycloheptyl, adamantyl, decalinyl, norbornyl, ...

- a trihalogeno(C_1-C_6)alkyl group denotes an alkyl group as defined above which contains a trihalogeno group ; examples of such groups without implying any limitation are trifluoromethyl, 2,2,2-trifluoroethyl, ...

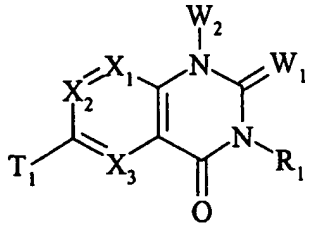
- a (C_1-C_6)acyl group denotes an alkyl group or a aryl group as defined above bound through a carbonyl group ; examples of such groups without implying any limitation are acetyl, ethylcarbonyl, benzoyl, ...
- a multiple bond denotes double bond or triple bond,
- optical isomers refer to racemates, enantiomers and diastereoisomers.

The invention also relates to the pharmaceutically acceptable salts of the compounds of formula (I). A review of the pharmaceutically acceptable salts will be found in *J. Pharm. Sci.*, 1977, 66, 1-19.

Pharmaceutically acceptable acids mean non-toxic mineral or organic acids. Among those there may be mentioned, without implying any limitation, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphonic acid, nitric acid, citric acid, acetic acid, trifluoroacetic acid, lactic acid, pyruvic acid, malonic acid, succinic acid, glutaric acid, fumaric acid, tartaric acid, maleic acid, ascorbic acid, oxalic acid, methanesulfonic acid, camphoric acid, benzoic acid, toluenesulfonic acid, etc...

Pharmaceutically acceptable bases mean non-toxic mineral or organic bases. Among those, there may be mentioned, without implying any limitation, sodium hydroxide, potassium hydroxide, calcium hydroxide, triethylamine, tert-butylamine, dibenzylethylenediamine, piperidine, pyrrolidine, benzylamine, quaternary ammonium hydroxides etc...

The invention also relates to a process for the preparation of compounds of formula (I), which uses as starting material a compound of formula (II):

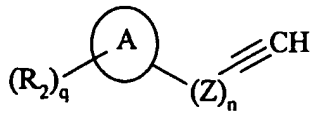


(II)

in which R_1, W_1, W_2, X_1, X_2 and X_3 have the same definitions as the compounds of formula (I), and T_1 represents a group selected from hydrogen, halogen, mesylate, triflate, formyl, acetyl, and ester,

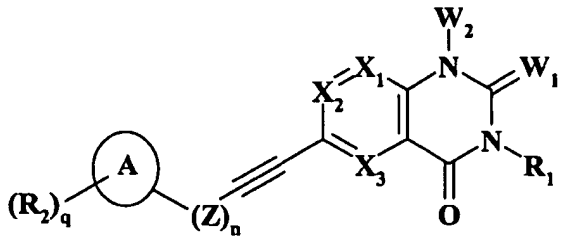
compound of formula (II) which is treated :

❖ either when T_1 represents an halogen atom, a mesylate group, or a triflate group, in the presence of a base under conditions of palladium-catalyzed alkynylation with a compound of formula (III):



(III)

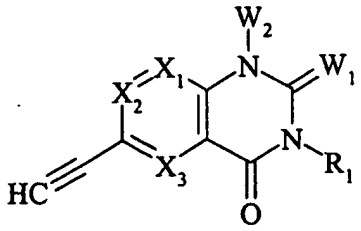
in which A, Z, R_2, q and n are as defined for the compounds of formula (I),
to yield the compounds of formula (I),



(I)

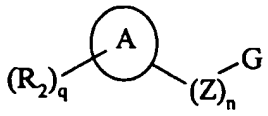
❖ or when T_1 represents an hydrogen atom, with iodine to yield *in situ* the corresponding iodide intermediate, which is treated directly without isolation or purification, with a compound of formula (III) as described hereinbefore, under conditions of palladium-catalyzed alkynylation in the presence of a base,
to yield the compounds of formula (I),

❖ or when T_1 represents an acetyl group, first with lithium diisopropylamine at -78°C in an inert solvent to provide an enolate, second with diethyl chlorophosphate and subsequently with lithium diisopropylamine, to yield a compound of formula (IV):



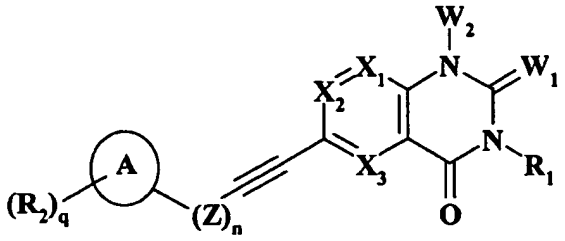
(IV)

in which R_1, W_1, W_2, X_1, X_2 and X_3 are as defined hereinbefore,
and condensing the compound of formula (IV), in the presence of triphenylphosphin and $PdCl_2(PPh_3)_2$, under basic conditions to a compound of formula (V):



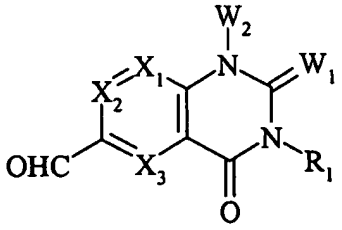
(V)

in which A, Z, R_2, q and n are as defined hereinbefore and G represents a leaving group, to yield the compound of formula (I),



(I)

❖ or when T_1 represents an ester group, with a reductive agent, to yield the corresponding aldehyde compound of formula (VI):

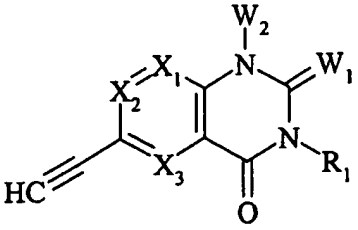


(VI)

in which R_1, W_1, W_2, X_1, X_2 and X_3 are as defined hereinbefore,

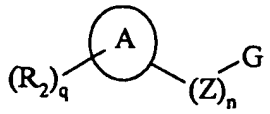
and subsequently :

- either condensing said compound of formula (VI), in basic conditions, with diazomethyl trimethyl silane or with diazomethyl diethoxy phosphonate, to yield, after basic treatment, a compound of formula (IV) as defined hereinbefore :



(IV)

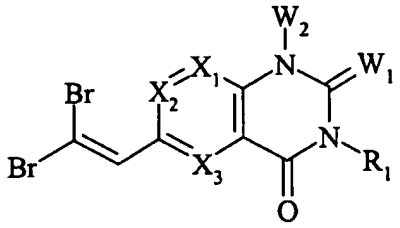
and adding said compound of formula (IV) to a compound of formula (V) as described hereinbefore :



(V)

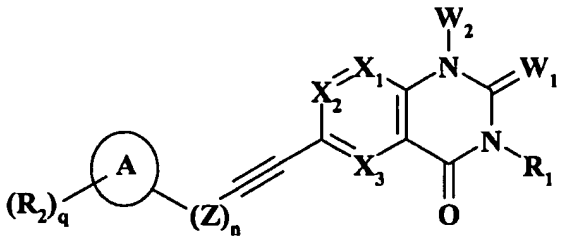
in which R_2, A, Z, q, n and G are as defined hereinbefore,
to yield the compound of formula (I),

- or reacting, said compound of formula (VI), with tetrabromomethane in the presence of triphenylphosphine in an aprotic solvent to yield a compound of formula (VII) :



(VII)

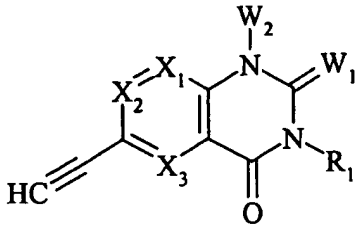
in which R_1, W_1, W_2, X_1, X_2 and X_3 are as defined hereinbefore,
and dehalogenating said compound of formula (VII) throug treatment with a strong base in an inert solvent, or with butyllithium in presence of triphenylphosphine and zinc, to yield the compound of formula (IV) as defined hereinbefore,
and reacting said compound of formula (IV) with a compound of formula (V) as defined in the previous step to yield a compound of a general formula (I):



(I)

The compound of formula (I) are purified, where appropriate, according to a conventional purification technique, and separated, where appropriate, into their different isomers according to a conventional separation technique, and converted, where appropriate, into addition salts thereof with a pharmaceutically-acceptable acid or base.

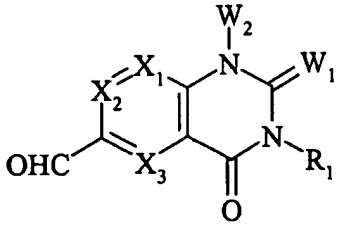
The compounds of formula (IV):



(IV)

wherein W_1, W_2, X_1, X_2, X_3 and R_1 are as defined in compounds of formula (I) are novel useful intermediates for the preparation of compounds of formula (I).

The compounds of formula (VI)

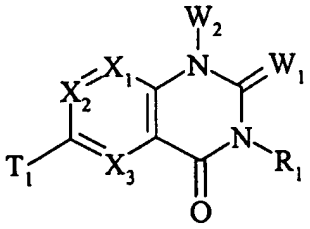


(VI)

wherein W_1, W_2, X_1, X_2, X_3 and R_1 are as defined in compounds of formula (I) are also novel useful intermediates for the preparation of compounds of formula (I).

The compounds of formula (II) used as starting material may be distinguished into two groups which are respectively represented :

- by the compounds of the formula (II/A) :



(II/A)

wherein :

W_1 represents an oxygen atom, a sulfur atom, or a $-NR_3$ group in which R_3 represents hydrogen atom, $(C_1\text{-}C_6)$alkyl, hydroxyl or cyano,

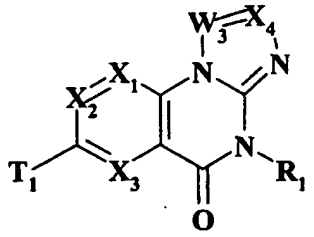
W_2 represents a group selected from :

- hydrogen atom, trifluoromethyl, amino, mono$(C_1\text{-}C_{10})$alkylamino, di$(C_1\text{-}C_{10})$alkylamino, each alkyl moiety being identical or different,

- (C_1-C_6)alkyl, (C_3-C_6)alkenyl, (C_3-C_6)alkynyl, (C_5-C_{10})aryl, (C_5-C_{10})aryl(C_1-C_{10})alkyl, (C_3-C_{10})cycloalkyl(C_1-C_{10})alkyl, and the residue of an aromatic or non aromatic heterocycle comprising 5 or 6 ring members including from 1 to 4 hetero atoms selected from nitrogen, oxygen and sulfur, these groups being optionally substituted by one or more groups, which may be identical or different, selected from halogen, amino, mono(C_1-C_{10})alkylamino, di(C_1-C_{10})alkylamino, each alkyl moiety being identical or different, cyano, trihalogeno(C_1-C_6)alkyl, (C_1-C_6)acyl, $-C(=O)OR_4$, $-OR_4$ and $-SR_4$, R_4 representing a hydrogen atom or a (C_1-C_6)alkyl group,

T_1 represents a group selected from hydrogen, halogen, mesylate, triflate, formyl, acetyl, and ester, and R_1, X_1, X_2, and X_3 are as defined in the compounds of formula (I),

➢ and by the compounds of formula (II/B) :



(II/B)

wherein :

W_3 represents a nitrogen atom or a group $-CR_5$ in which R_5 is selected from :

- a hydrogen atom,
- $-OR_6$, $-SR_6$ in which R_6 is selected from hydrogen, (C_1-C_6)alkyl and (C_5-C_8)aryl(C_1-C_{10})alkyl;
- (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, the residue of a saturated heterocycle comprising from 3 to 8 ring members including one hetero atom selected from oxygen, sulfur and nitrogen, (C_5-C_8)aryl, (C_5-C_8)heteroaryl comprising from 1 to 4 hetero atoms selected from oxygen, sulfur and nitrogen, and (C_5-C_8)aryl(C_1-C_{10})alkyl, these groups being optionally substituted by $-(CH_2)_p-OH$ or $-(CH_2)_p-NH_2$, wherein p is an integer from 0 to 4 inclusive,

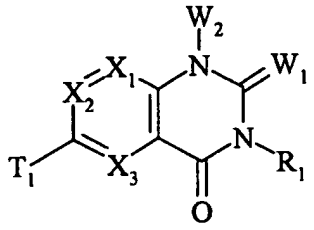
X_4 represents a nitrogen atom or a group $-CR_7$ in which R_7 is selected from hydrogen, $-NR_8R_9$, $-OR_8$, $-SR_8$, (C_1-C_6)alkyl, (C_3-C_{10})cycloalkyl, the residue of a saturated heterocycle comprising from 3 to 8 ring members including one hetero atom selected from oxygen, sulfur and nitrogen, (C_5-C_{10})aryl, (C_5-C_{10})heteroaryl comprising from 1 to 4 hetero atoms selected from oxygen, sulfur and nitrogen, and (C_5-C_{10})aryl(C_1-C_{10})alkyl, these groups being optionally substituted by $-(CH_2)_p-OH$ or $-(CH_2)_p-NH_2$ wherein p is an integer from 0 to 4 inclusive,

and in which R_8 and R_9, identical or different, are selected from hydrogen, (C_1-C_6)alkyl and (C_5-C_{10})aryl(C_1-C_{10})alkyl,

T_1 represents a group selected from hydrogen, halogen, mesylate, triflate, formyl, acetyl, and ester, and R_1, X_1, X_2, and X_3 are as defined in the compound of formula (I).

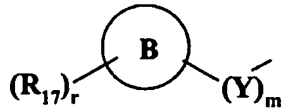
In an advantageous embodiment of the invention, the process for the preparation of compounds of formula (I) comprises the following step :

- reacting as starting material, a compound of formula (II/A) :



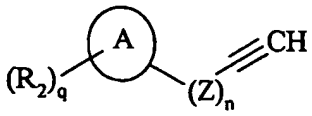
(II/A)

in which W_1 represents an oxygen atom, W_2 represents a (C_1-C_6)alkyl group, X_1 represents a -CH group, X_2 represents a nitrogen atom or a -CH group, X_3 represents a -CH group, and T_1 represent a iodine atom or a triflate group, and R_1 represents a group of formula :



in which Y represents a methylene group, m is equal to one, B represents a phenyl group, R_{17} is as defined in the compound of formula (I) and r is equal to one,

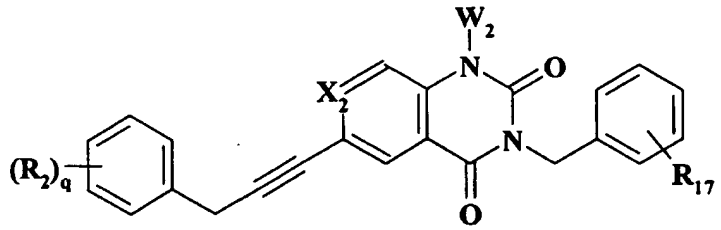
- with, as reagent, a compound of formula (III) :



(III)

in which Z represents a methylene group, n is equal to one, A is a phenyl group, q is equal to zero or one, and R_2 is as defined in the compound of formula (I),

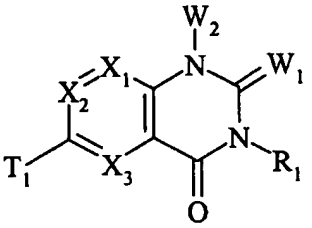
to yield a compound of formula (I/a), which constitutes a particular subgroup of the compounds of formula (I):



(I/a)

in which W_2, X_2, R_2, q and R_{17} are as defined hereinbefore.

The compounds of formula (II/A)



(II/A)

wherein :

W_1 represents an oxygen atom, a sulfur atom, or a $-NR_3$ group in which R_3 represents hydrogen atom, $(C_1\text{-}C_6)$alkyl, hydroxyl or cyano,

W_2 represents a group selected from :

- hydrogen atom, trifluoromethyl, amino, mono$(C_1\text{-}C_{10})$alkylamino, di$(C_1\text{-}C_{10})$alkylamino, each alkyl moiety being identical or different,
- $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$alkenyl, $(C_3\text{-}C_6)$alkynyl, $(C_5\text{-}C_{10})$aryl, $(C_5\text{-}C_{10})$aryl$(C_1\text{-}C_{10})$alkyl, $(C_3\text{-}C_{10})$cycloalkyl$(C_1\text{-}C_{10})$alkyl, and the residue of an aromatic or non aromatic heterocycle comprising 5 or 6 ring members including from 1 to 4 hetero atoms selected from nitrogen, oxygen and sulfur, these groups being optionally substituted by one or more groups, which may be identical or different, selected

from halogen, amino, mono(C_1-C_{10})alkylamino, di(C_1-C_{10})alkylamino, each alkyl moiety being identical or different, cyano, trihalogeno(C_1-C_6)alkyl, (C_1-C_6)acyl, -C(=O)OR_4, -OR_4 and -SR_4, R_4 representing a hydrogen atom or a (C_1-C_6)alkyl group,

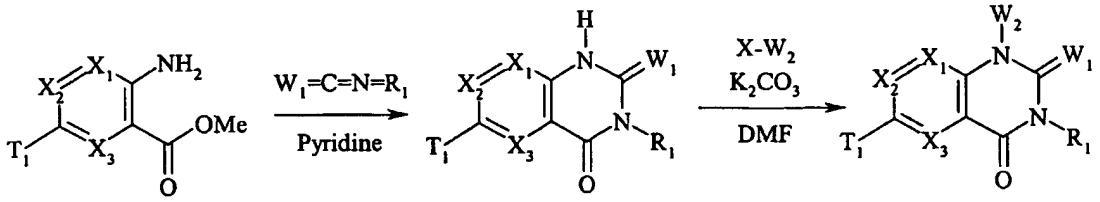
T_1 represents a halogen atom,

and R_1, X_1, X_2, and X_3 are as defined in the compounds of formula (I),

are also novel useful intermediates for the preparation of compounds of formula (I).

The compounds of formula (II/A) may be obtained through the synthetic way described in scheme 1.

Scheme 1



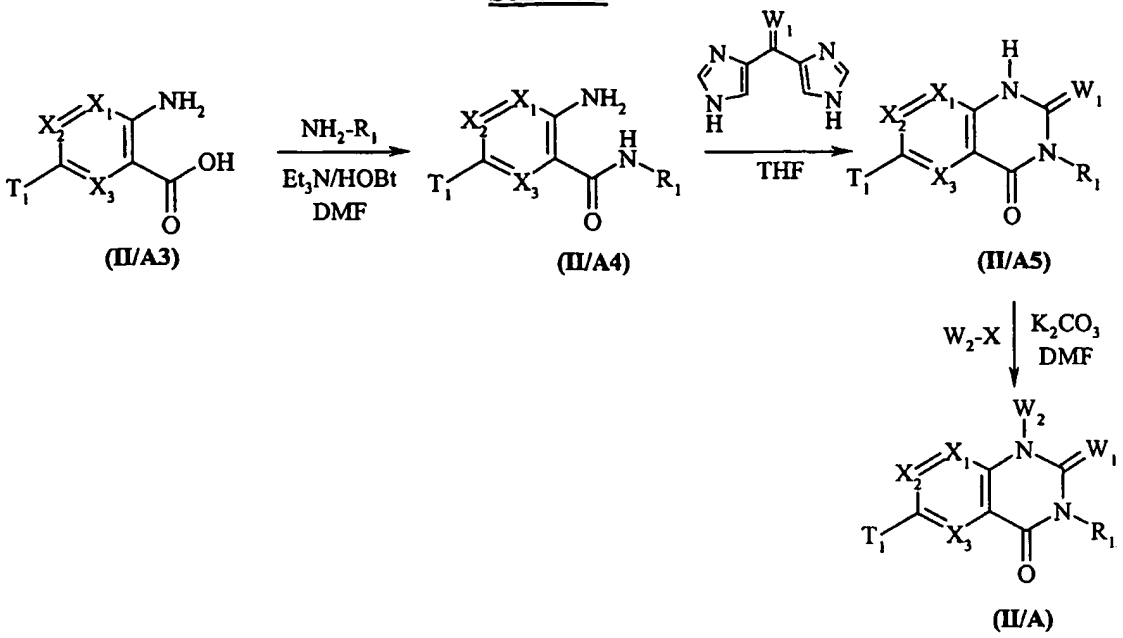
(II/A1) (II/A2) (II/A)

In these compounds of formulae (II/A1) and (II/A2), the substituents X_1, X_2, X_3, W_1, W_2, R_1 and T_1 are as defined in the compounds of formula (II/A). In the compound X-W_2, W_2 is as defined hereinbefore and X represents a leaving group.

The starting material (II/A1) is either a commercial product or is obtained according to conventional methods of organic synthesis well known to the person skilled in the art.

In another preferred embodiment, compounds of formula (II/A), where W_1 represents an oxygen atom or a sulfur atom, may be obtained through the synthetic way described in scheme 2.

Scheme 2

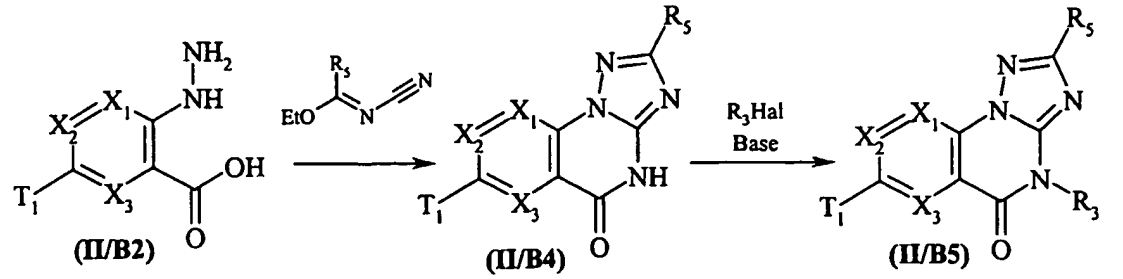


(II/A3) (II/A4) (II/A5) (II/A)

In a first step the acid function of compound (II/A3) is transformed into an amide group by reaction with a primary amine in usual conditions of organic chemistry to yield the compound (II/A4). This intermediate is then treated with 1,1'-carbonyldiimidazole or 1,1'-thiocarbonyldiimidazole, depending whether of W_1 is an oxygen atom or a sulfur atom, in anhydrous tetrahydrofuran, to yield a compound of formula (II/A5), which is treated in the same conditions as those described in scheme 1 to obtain the compound of formula (II/A).

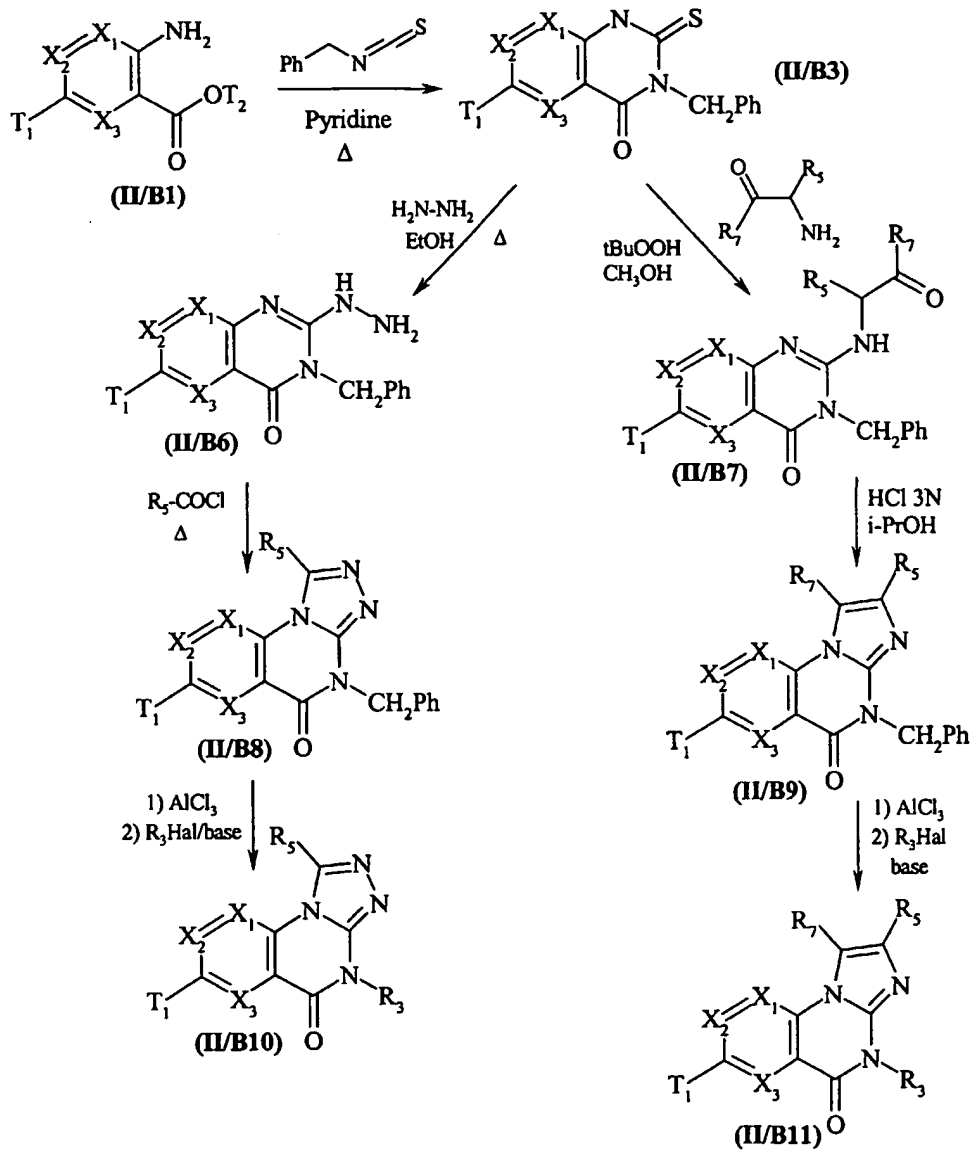
Compounds of the formula (II/B) are obtained through the synthetic way described in scheme 3 and in scheme 4.

Scheme 3



(II/B2) (II/B4) (II/B5)

Scheme 4



In Scheme 3 the compound (II/B5) is obtained from substrate (II/B2) which is commercially available or obtained through usual methods of organic synthesis. The compound (II/B2) is treated with an alkyl *N*-cyanoimidate to give a compound of formula (II/B4). The substitution of NH in position 4 with a halide in the presence of a base like cesium carbonate in an aprotic solvent leads to the formation of a compound of formula (II/B5) which represents a particular subgroup of compounds of formula (II) used as starting material in the general process for manufacturing compounds of formula (I).

In Scheme 4 the compound (II/B10) is obtained starting from compound (II/B1) which is treated in a first step with benzyl isothiocyanate to give the thiocarbonyl derivative (II/B3). This compound is heated, in a refluxing alcohol, in the presence of hydrazine hydrate to give the corresponding hydrazine (II/B6) which is in turn cyclized by reaction with an acid chloride or an orthoester to yield compound of formula (II/B8). This compound is then debenzylated by usual treatment and the N4-debenzylated atom is substituted by a halide in a basic medium, for example by addition of cesium carbonate in dimethylformamide to yield the product of formula (II/B10). The compound of formula (II/B10) is a particular subgroup of the compounds of formula (II) used as starting material in the general process for manufacturing compounds of formula (I).

In Scheme 4, the compound (II/B11) is obtained starting from compound (II/B1) which is transformed in a first step into a compound of formula (II/B3) as described hereinbefore. This compound (II/B3) is then treated in an alcoholic solvent such as methanol or ethanol, in the presence of a peroxide for initiating the oxidation of the starting thiol. The amino ketone (II/B6) obtained thereby is readily cyclized in the presence of acid, in an alcoholic solvent such as *iso*propanol to yield a compound of formula (II/B9) which is debenzylated and subsequently substituted on the N4 as described hereinbefore in order to obtain the product of formula (II/B11). The compound of formula (II/B11) is a particular subgroup of the compounds of formula (II) used as starting material in the general process for manufacturing compounds of formula (I).

Generally, isomers of the compounds of the invention are understood to be optical isomers such as enantiomers and diastereoisomers. More especially, pure enantiomeric forms of the compounds of the invention may be separated by starting from mixtures of enantiomers which are reacted with a racemate-separating agent that can be released, the said agent being itself in the form of a pure enantiomer, which allows the corresponding diastereoisomers to be obtained. The diastereoisomers are then separated according to the separation techniques well known to the person skilled in the art, such as crystallization or chromatography, and the separating agent is then removed using conventional techniques of organic synthesis, resulting in a pure enantiomer.

The compounds of the invention that are present in the form of a mixture of diastereoisomers are isolated in a pure form by using conventional separation techniques such as chromatography.

As mentioned above, compounds of formula (I) of the present invention are matrix metalloprotease inhibitors, and more particularly inhibitors of the enzyme MMP-13.

In this respect, their use is recommended for the treatment of diseases or complaints involving a therapy by MMP-13 inhibition. By way of example, the use of the compounds of the present invention may be recommended for the treatment of any pathology in which destruction of extracellular matrix tissue occurs, and most particularly pathologies such as arthritis, rheumatoid arthritis, osteoarthritis, osteoporosis, periodontal diseases, inflammatory bowel disease, psoriasis, multiple sclerosis, cardiac insufficiency, atherosclerosis, asthma, chronic obstructive pulmonary disease, age-related macular degeneration and cancers.

The present invention also relates to pharmaceutical compositions comprising as active ingredient at least one compound of formula (I), an isomer thereof, a N-oxide thereof, or an addition salt thereof with a pharmaceutically-acceptable acid or base, alone or in combination with one or more pharmaceutically-acceptable, inert, non-toxic excipients or carriers.

Among the pharmaceutical compositions according to the invention, there may be mentioned more especially those that are suitable for oral, parenteral (intravenous, intramuscular or subcutaneous), per- or trans-cutaneous, intravaginal, rectal, nasal, perlingual, buccal, ocular or respiratory administration.

Pharmaceutical compositions according to the invention for parenteral injections especially include aqueous and non-aqueous sterile solutions, dispersions, suspension and emulsions, and also sterile powders for reconstituting injectable solutions or dispersions.

Pharmaceutical compositions according to the invention for oral administration in solid form especially include tablets or dragées, sublingual tablets, sachets, gelatin capsules and granules, for oral, nasal, buccal or ocular administration in liquid form, especially include emulsions, solutions, suspensions, drop, syrups and aerosols.

Pharmaceutical compositions for rectal or vaginal administration are preferably suppositories, and those for per- or trans-cutaneous administration especially include powders, aerosols, creams, ointment, gels and patches.

The pharmaceutical compositions mentioned hereinbefore illustrate the invention but do not limit it in any way.

Among the pharmaceutically acceptable, inert, non-toxic excipients or carriers there may be mentioned, by way of non-limiting example, diluents, solvents, preservatives, wetting agents, emulsifiers, dispersing agents, binders, swelling agents, disintegrating agents, retardants, lubricants, absorbents, suspending agents, colourants, aromatizing agents etc...

The useful dosage varies according to the age and weight of the patient, the administration route, the pharmaceutical composition used, the nature and severity of the disorder and the administration of any associated treatments. The dosage ranges from 2 mg to 1 g per day in one or more administrations. The compositions are prepared by methods that are common to those skilled in the art and generally comprise 0.5% to 60% by weight of active principle (compound of formula (I)) and 40% to 99.5% by weight of pharmaceutically acceptable excipients or carriers.

The examples that follow illustrate the invention but do not limit it in any way.

The starting materials used are products that are known or that are prepared according to known operating procedures. The various preparations yield synthetic intermediates that are useful in preparation of the compounds of the invention. Some of these intermediates are new compounds.

The structures of the compounds described in the Examples and Preparations were determined according to the usual spectrophotometric techniques (infrared, nuclear magnetic resonance, mass spectrometry, ...)

In the Preparations and Examples, it is understood that :

- DMF means Dimethylformamide,
- THF means Tetrahydrofurane,
- DMSO means Dimethylsulfoxyde,
- TOTU means O-(ethoxycarbonyl)cyanomethylamino]-*N-N-N'-N'*-tetramethyl uronium fluoroborate

EXAMPLES

Preparation A : 4-(6-Iodo-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin-3-ylmethyl)-benzoic acid

Step 1 : Methyl 4-[(2-amino-5-iodo-benzoylamino)-methyl]-benzoate

To a stirred solution of 15 g (74.4 mmol) of methyl 4-(aminomethyl)benzoate hydrochloride, 300 ml of dimethylformamide and 10.3 ml (7.53g, 74.4 mmol) of triethylamine were added, at room temperature, followed by 10.06 g (74.4 mmol) of 1-hydroxybenzotriazole hydrate, 19.6 g (74.4 mmol) of 2-amino-5-iodobenzoic acid and 14.3 g (74.4 mmol) of 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride. After stirring at room temperature overnight, the mixture was concentrated and the residue was dissolved in 300 ml of dichloromethane. The organic phase was washed with 150 ml H_2O, 150 ml HCl 1N, and 150 ml H_2O, dried over sodium sulfate and concentrated. The residue was recrystallized from 170 ml acetonitrile to afford after filtration 19.6 g of the desired product (yield : 70%).

N.M.R: DMSO ^1H δ (ppm) : 3.8 (s,3H); 4.45 (d,2H); 6.5-6.6 (m,3H); 7.3-7.45 (m,3H); 7.8-7.95 (m,3H); 8.9 (t,1H)

Purity (HPLC) : 99.1 %

Step 2 : Methyl 4-(6-iodo-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl)-benzoate

To a solution of 21.35 g (52 mmol) of the compound obtained in Step 1 in 400 ml of dry tetrahydrofurane were added 9.3 g (57.2 mmol) of 1,1'-carbonyldiimidazole.The solution was heated overnight to 60°C. After cooling the precipitate was filtered and dried to afford 19.6 g of the desired product (yield : 68.3%).

N.M.R: DMSO ^1H δ (ppm) : 3.8 (s,3H); 5.1 (s,2H); 6.95-7.05 (m,1H); 7.35-7.45 (m,2H); 7.8-7.90 (m,2H) ; 7.9-8.0 (m,1H) ; 8.2 (s,1H) ; 11.6 (bs,1H)

Purity (HPLC) : 99.5 %

Step 3 : Methyl 4-(6-iodo-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl) -benzoate

To a stirred suspension of 11 g (25.2 mmol) of the compound obtained in Step 2 and 110 ml of dry DMF were added 5.22 g (37.8 mmol) of K_2CO_3, at room temperature. After 15 minutes, 7.85 ml (17.9 g, 126 mmol) of iodomethane were added. The reaction mixture was stirred for 2 hours and the precipitate filtered off and dissolved in a mixture of dichloromethane/methanol. The organic phase was washed with H_2O, dried over Na_2SO_4 and concentrated to afford a precipitate corresponding to the desired product (10.1 g ; yield : 89%).

N.M.R: DMSO ^1H δ (ppm): 3.5 (s,3H); 3.8 (s,3H); 5.2 (s,2H); 7.30 (d,1H); 7.45 (d,2H) ; 7.90 (d,2H) ; 8.1 (d,1H) ; 8.3 (s,1H)

Purity (HPLC) : 96.7 %

Step 4 : 4-(6-Iodo-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl)-benzoic acid

A mixture of 3.0 g (6.66 mmol) of the compound obtained in Step 3, 30 ml of dioxane, 120 ml H_2O, and 0.56 g (13.3 mmol) of $LiOH,H_2O$ was heated to reflux over 1 hour. After cooling and acidification with concentrated hydrochloric acid, the precipitate obtained was filtered off and recrystallized in dioxane/ether to afford 1.85 g of the desired product (yield : 64.2%).

N.M.R: DMSO ^1H δ (ppm): 3.5 (s,3H); 5.2 (s,2H); 7.30 (d,1H);7.40 (d,2H); 7.85 (d,2H) ; 8.1 (d,1H) ; 8.30 (s,1H) ; 12.9 (bs,1H)

Purity (HPLC) : 98.0 %

Preparation B : 4-(1-Methyl-2,4-dioxo-6-trifluoromethanesulfonyloxy-1,4-dihydro-2H-pyrido[3,4-d]pyrimidin-3-ylmethyl)-benzoic acid

Step 1 : 5-(*tert*-Butoxycarbonylamino)-2-methoxypyridine-4-carboxylic acid

The compound 5-(*tert*-butoxycarbonylamino)-2-methoxypyridine-4-carboxylic acid was prepared using the procedure described in *J. Chem. Soc., Perkin Trans I*, 1996, 18, 2221-2226.

Step 2 : Methyl 4-{[(5-*tert*-butoxycarbonylamino-2-methoxy-pyridine-4-carbonyl)-amino]-methyl}-benzoate

9 g (33.5 mmol) of the compound obtained in Step 1, 320 ml of dichloromethane, 11 g (33.5 moles) of TOTU and 6.1 g (36.9 mmol) of methyl-(4-aminomethyl)benzoate were stirred and cooled to 0°C, and then 11.6 ml (8.6g, 67 mmol) of diisopropylamine added. The mixture was stirred for 15 minutes at 0°C and then overnight at room temperature. The reaction mixture was washed successively with 200 ml NH_4OH, 200 ml H_2O, 200 ml HCl 10%, 200 ml H_2O, 200 ml $NaHCO_3$, and 200 ml H_2O. The organic phase was dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was crystallized in a mixture of dichloromethane/ether to afford 10.5 g of the desired product (yield : 73.3 %).

TLC : CH_2Cl_2/MeOH: 95/5 v/v Rf = 0.60

N.M.R: $CDCl_3$ ^1H δ (ppm) : 1.50 (s,9H) ; 3.90 (2s,6H) ; 4.60 (d,2H) ; 6.70 (s,1H) ; 7.0 (bs,1H) ; 7.4 (d,2H) ; 8.0 (d,2H) ; 8.75 (bs,1H) ; 8.9 (s,1H)

Step 3 : Methyl 4-{[(5-amino-2-methoxy-pyridine-4-carbonyl)-aminomethyl}-benzoate

To a solution of 4.8 g (11.5 mmol) of the compound obtained in Step 2 in 100 ml of dichloromethane were added 20 ml of trifluoroacetic acid. The reaction was heated to 40°C for 1 hour, and then concentrated under vacuum. The residue was taken up in a mixture of dichloromethane and H_2O then basified with NaOH. After separation by decantation, the organic phase was washed, dried over Na_2SO_4, and concentrated under vacuum to afford 3.5 g of a yellow precipitate corresponding to the desired product (yield : 97%).

TLC : CH_2Cl_2/MeOH 95/5 v/v Rf = 0.40

N.M.R: $CDCl_3$ ^1H δ (ppm) : 3.8 (s,3H) ; 3.9 (s,3H) ; 4.6 (d,2H) ; 4.7 (s,2H) ; 6.7 (s,1H) ; 6.75-6.85 (m,1H) ; 7.40 (d,2H) ; 7.75 (s,2H) ; 8.0 (d,2H)

Step 4 : Methyl 4-(6-methoxy-2,4-dioxo-1,4-dihydro-2*H*-pyrido[3,4-*d*]-pyrimidin-3-ylmethyl)-benzoate

To a solution of 2.5 g (7.9 mmol) of the compound obtained in Step 3 in 110 ml of dry THF were added 2 g (12.4 mmol) of 1,1'-carbonyldiimidazole. The reaction mixture was heated to 60°C for 24 hours. After cooling, 50 ml H_2O were added and the mixture was stirred for 30 minutes to 0°C. The precipitate was filtered and washed successively with H_2O, MeOH and dichloromethane to afford 2.38 g of the desired product (yield : 88.3%).

TLC : CH_2Cl_2/MeOH 95/5 v/v Rf = 0.45

N.M.R: DMSO ^1H δ (ppm) : 3.80 (s,3H) ; 3.90 (s,3H) ; 5.10 (s,2H) ; 7.2 (s,1H) ; 7.45 (d,2H) ; 7.90 (d,2H) ; 8.25 (s,1H) ; 11.6 (s,1H)

Step 5 : Methyl 4-(6-methoxy-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-pyrido[3,4-*d*]pyrimidin-3-ylmethyl)-benzoate

2.38 g (7 mmol) of the compound obtained in Step 4 and 52 ml of dry DMF were stirred and heated until dissolution. After cooling to 25°C, 1.45 g (10 mmol) of K_2CO_3 and 2.2 ml (5.7 g, 35 mmol) of iodomethane were added. The mixture was stirred for 30 minutes at room temperature, then concentrated under vacuum. The residue was treated with H_2O and the precipitate filtered off, washed with methanol, then dissolved in dichloromethane. The organic phase was washed with H_2O, dried over Na_2SO_4 and concentrated under vacuum. The product was crystallised in ether and filtered to afford 2.0 g of the desired product (yield : 80%).

TLC : CH_2Cl_2/MeOH 95/5 v/v Rf = 0.95

Purity (HPLC) : 98.5%

N.M.R: DMSO ^1H δ (ppm) : 3.50 (s,3H) ; 3.80 (s,3H) ; 3.90 (s,3H) ; 5.20 (s,2H) ; 7.3 (s,1H) ; 7.45 (d,2H) ; 7.90 (d,2H) ; 8.50 (s,1H)

Step 6 : 4-(6-Hydroxy-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-pyrido[3,4-*d*]pyrimidin-3-ylmethyl)-benzoic acid

1.4 g (3.93 mmol) of compound obtained in Step 5, and 14 ml of hydrobromic acid were heated to reflux for 1 hour. After cooling, 30 ml of H_2O were added and the precipitate was filtered off and washed with H_2O and MeOH to afford 1.1 g of the desired product (yield : 85.5%)

TLC : CH_2Cl_2/MeOH 90/10 v/v Rf = 0.10

N.M.R : DMSO ^1H δ (ppm) 3.50 (s,3H); 5.20 (s,2H) ; 7.05 (s,1H) ; 7.40 (d,2H) ; 7.90 (d,2H) ; 8.20 (s,1H) ; 10.4-13.0 (bs,2H)

Step 7 : 4-(1-Methyl-2,4-dioxo-6-trifluoromethanesulfonyloxy-1,4-dihydro-2*H*-pyrido[3,4-*d*]pyrimidin-3-ylmethyl)-benzoic acid

A solution of 1.2 g of compound obtained in Step 6 in 14 ml of dry pyridin was stirred and cooled to 0°C, and then 1.5 ml (2.52 g, 9 mmol) of trifluoromethanesulfonic anhydride were added. The reaction was allowed to stir at 0°C for 30 minutes then quenched with 30 ml of H_2O and dichloromethane. The organic phase was washed with H_2O, HCl 10%, and H_2O. After concentration the residue was crystallised in a mixture dichloromethane/ether to afford 0.5 g of the desired product (yield : 30%).

TLC : CH_2Cl_2/MeOH 90/10 v/v Rf = 0.55

N.M.R: DMSO ^1H δ (ppm): 3.55 (s,3H) ; 5.20 (s,2H) ; 7.45 (d,2H) ; 7.90 (d,2H) ; 8.10 (s,1H) ; 8.80 (s,1H) ; 12.9 (bs,1H)

***Preparation C :* Methyl 4-(5-oxo-7-(Trifluoromethylsulfonyloxy)-5*H*-[1,2,4]triazolo [4,3-*a*]quinazolin-4-ylmethyl)-benzoate**

Step 1 : 4-Benzyl-7-(trifluoromethylsulfonyloxy)-4*H*-[1,2,4]triazolo[4,3*a*]quinazolin -5-one

To a suspension of 41.3 g (141.3 mmol) of 4-benzyl-7-hydroxy-4*H*-[1,2,4]triazolo[4,3-*a*]quinazolin-5-one (obtained as described in WO 00/66584) in 500 ml of CH_2Cl_2, 25 g (148.3 mmol) of trifluoromethylsulfonylchloride were added under stirring. Then, 22.5 g (222.5 mmol) of triethylamine were added dropwise while maintaining the internal temperature between 15 and 20°C. After the completion of addition, stirring was continued at room temperature for 4 hours. After removal of the insoluble solid by filtration, the organic solution was washed with water and brine, then dried over Na_2SO_4 and

concentrated, providing 33.1 g of crude solid, which was purified by chromatography (cyclohexane/AcOEt: 25/75 v/v) to afford 22.5 g of the desired compound (yield : 37.5%).
TLC : CH_2Cl_2/MeOH 95/5 v/v Rf = 0.45

Step 2 : 7-(Trifluoromethylsulfonyloxy)-4*H*-[1,2,4]triazolo[4,3-*a*]quinazolin-5-one

A suspension of 10.0 g (23.5 mmol) of the compound obtained in Step 1 and 18.8 g (141 mmol) of aluminium chloride in 200 ml anhydrous benzene was heated at 50°C, under stirring, for 1h30. After cooling, the mixture obtained was poured on water/ice. After stirring and homogenization, the insoluble solid was isolated by filtration, washed with several portions of water until neutral pH and dried, then finally washed with a portion of CH_2Cl_2, leaving 7.95 g (99%) of the desired compound.
TLC : CH_2Cl_2/MeOH 95/5 v/v Rf = 0.10

Step 3 : Methyl 4-(5-oxo-7-(Trifluoromethylsulfonyloxy)-5*H*-[1,2,4]triazolo[4,3-*a*] quinazolin-4-ylmethyl)-benzoate

To a stirred solution of 7.9 g (24.3 mmol) of the compound obtained in Step 2 in 100 ml of DMF were added 7.93 g (24.3 mmol) of cesium carbonate, and then 5.56 g (24.3 mmol) of methyl 4-(bromomethyl)benzoate. The mixture was stirred overnight and the solvent was removed under vacuum. The resulting residue was partitioned between H_2O and a mixture of dichloromethane and ethyl acetate. A first portion (5.9 g) of product insoluble in the two phases was obtained by filtration then recrystallized in methanol to give 4.85 g of the pure title compound. The organic phase was separated, washed with water and brine, and dried over anhydrous sodium sulfate. Concentration under reduced pressure afforded 4.5 g of crude product that was recrystallized in methanol to provide 2.2 g of pure compound. An additional portion of 2.5 g was finally obtained after column chromatography on silica gel of the residues gathered from the organic phases (dichloromethane/methanol 98/2 v/v). All in all, 9.55 g (yield : 81.5%) of the desired product were obtained.
TLC : CH_2Cl_2/CH3OH 95/5 v/v Rf = 0.35

Preparation D : 4-(5-oxo-7-(Trifluoromethylsulfonyloxy)-5H-[1,2,4]triazolo[4,3-a] quinazolin-4-ylmethyl)-benzoic acid

Step 1 : ***tert*-Butyl 4-(5-oxo-7-(Trifluoromethylsulfonyloxy)-5*H*-[1,2,4]triazolo [4,3-*a*]quinazolin-4-ylmethyl)-benzoate**

The product is obtained with a yield of 60.5% (0.95 g) according to the procedure of Step 3 of Preparation C using 1.0 g (2.99 mmol) of compound obtained in Step 1 of Preparation C and 0.81 g (2.99 mmol) of *tert*-butyl-4-(bromomethyl)benzoate.

Step 2 : 4-(5-oxo-7-(Trifluoromethylsulfonyloxy)-5*H*-[1,2,4]triazolo[4,3-*a*] quinazolin-4-ylmethyl)-benzoic acid

To a suspension of 0.27 g (0.515 mmol) of compound obtained in Step 1 in 30 ml of dichloromethane, 2.7 ml of trifluoroacetic acid were added and stirring was continued at room temperature for 16 hours. The reaction mixture was poured into water and the resulting mixture stirred for 15 minutes. The ensuing precipitate was filtered off, washed with water until neutral pH and dried at 50°C under vacuum to provide 0.21 g of the desired product.

TLC : dichloromethane/methanol 90/10 v/v Rf = 0.30

Example 1 : Methyl 4-{6-[3-(4-methoxyphenyl)-prop-1-ynyl]-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl}-benzoate

To a stirred suspension of 1.5 g (3.33 mmol) of compound obtained in Step 3 of Preparation A in 110 ml of triethylamine were added, under nitrogen atmosphere, 0.6 g (4 mmol) of 3-(4-methoxyphenyl)-prop-1-yne (described in the literature: *J.Prakt.Chem.*,1966, 33, 84-95) in 10 ml of triethylamine, 47 mg (0.06 mmol) of dichlorobis(triphenylphosphine)palladium (II) and 26 mg (0.13 mmol) of CuI. The mixture was heated to 60°C over 3 hours (uncomplete reaction). The mixture was then concentrated under vacuum and the residue purified by flash chromatography to afford 0.130 mg of the desired product (yield : 6%) which was crystallized in a mixture of dichloromethane/methanol.

TLC : CH_2Cl_2/Acetone 99/1 v/v Rf = 0.9

N.M.R: DMSO ^1H δ (ppm) ; 3.5 (s,3H); 3.75 (s,3H); 3.8 (s,5H); 5.2 (s,2H); 6.9 (d,2H); 7.35 (s,2H); 7.45 (m,3H); 7.85 (d,1H); 7.9 (d,2H); 8.0 (s,1H)

IR : 2361, 1702, 1656, 1612, 1508, 1475, 1279, 1249, 117, 1102, 958, 805 cm^{-1}

Mp = 168.5°C

Purity (HPLC) : 97.9 %

Example 2 : 4-[1-Methyl-2,4-dioxo-6-(3-phenyl-prop-1-ynyl)-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoic acid

To a stirred solution of 0.68 g (1.56 mmol) of compound obtained in Step 4 of Preparation A in 6.8 ml of dry DMF, were added successively, under nitrogen atmosphere, 1.2 ml (0.8 g, 6.24 mmol) of diisopropylethylamine, 56.8 mg (0.078 mmol) of dichlorobis (triphenylphosphine)palladium (II), a catalytic amount of CuI and 0.273 ml (0.253 g, 2.18 mmol) of 3-phenyl-1-propyne. The reaction mixture was heated to 50°C over approximately 4 hours. Then, the mixture is concentrated under vacuum and the residue purified by flash chromatography (dichloromethane/MeOH 90/10 v/v) to afford, after crystallization in a mixture of dichloromethane/ether, 0.270 g of the desired product (yield : 40.8%).

TLC : CH_2Cl_2/MeOH 9/1 v/v Rf = 0.50

N.M.R: DMSO ^1H δ (ppm) ; 3.5 (s,3H); 3.9 (s,2H); 5.2 (s,2H); 7.20-7.50 (m,8H); 7.80 (m,3H); 8.05 (s,1H); 12.8 (bs,1H);

IR : 2894, 1700, 1660, 1616, 1508,1314, 1295, 1097, 825, 795, 747 cm^{-1}

Mp = 258 °C

Purity (HPLC) : 98.6 %

Example 3 : 4-{6-[3-(4-Methoxy-phenyl)-prop-1-ynyl]-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl}-benzoic acid

This compound was obtained according to the procedure described in Example 2 using as reagent 3-(4-methoxyphenyl)-prop-1-ynyl. The crude product was crystallized in dioxane to afford the desired compound.

TLC : CH_2Cl_2/MeOH 9/1 v/v Rf = 0.50

N.M.R: DMSO ^1H δ (ppm) ; 3.55 (s,3H); 3.75 (s,3H); 3.8 (s,2H); 5.15 (s,2H); 6.9 (d,2H); 7.30 (d,2H); 7.40 (m,3H); 7.85 (m,3H); 8.00 (s,1H); 12.85 (bs,1H);

IR : 2646, 1687, 1659, 1508, 1477, 1422, 1325, 1242, 1177, 1040, 950, 812 cm^{-1}

Mp = 262 °C

Purity (HPLC) : 95.4 %

Example 4 : 4-[1-Methyl-2,4-dioxo-6-(3-phenyl-prop-1-ynyl)-1,4-dihydro-2*H*-pyrido[3,4-*d*]pyrimidin-3-ylmethyl]-benzoic acid

To a stirred solution of 0.1 g (0.22 mmol) of the compound of Preparation B in 1 ml of dry DMF were added successively 0.2 ml (0.14 g, 1.1 mmol) of diisopropylethylamine, 9 mg (0.012 mmol) of dichlorobis(triphenylphosphine)palladium (II), a catalytic amount of CuI and 0.046 ml (0.043 g, 1.1 mmol) of 3-phenyl-1-propyne. The reaction was stirred overnight at room temperature and then H_2O and CH_2Cl_2 were added. The organic layer was separated and washed with HCl 10% and H_2O, then dried over sodium sulfate and concentrated under vacuum. The residue was crystallized in a mixture of dichloromethane/ether to afford 0.040 g of the desired product (yield : 43%).

TLC : CH_2Cl_2/MeOH 9/1 v/v Rf = 0.50

N.M.R: DMSO ^1H δ (ppm) ; 3.6 (s,3H); 3.95 (s,2H); 5.2 (s,2H); 7.20-7.50 (m,7H); 7.80-7.95 (m,2H); 7.95 (s,1H); 8.90 (s,1H); 12.8 (bs,1H)

IR : 1720, 1695, 1678, 1612, 1490, 1279, 1100, 759, 732 cm^{-1}

Mp = 236.2 °C

Purity (HPLC) : 96.7 %

Example 5: 4-{6-[3-(4-Methoxy-phenyl)-prop-1-ynyl]-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-pyrido[3,4-*d*]pyrimidin-3-ylmethyl}-benzoic acid

The compound is obtained according to the procedure described in Example 4 using the compound of Preparation B and the 3-(4-methoxyphenyl)-prop-1-yne.

TLC : CH_2Cl_2/MeOH 9/1 v/v Rf = 0.60

N.M.R: DMSO ^1H δ (ppm); 3.60 (s,3H); 3.75 (s,3H); 3.85 (s,2H); 5.20 (s,2H); 6.9-7.0 (m,2H); 7.30-7.40 (m,2H); 7.45-7.50 (m,2H); 7.80-7.90 (m,3H); 8.90 (s,1H); 12.9 (bs,1H)

IR : 1721, 1670, 1511, 1477, 1421, 1325, 1245, 1178, 1037, 792 cm^{-1}

Mp = 262 °C

Purity (HPLC) : 95.9 %

Example 6 : 4-Benzyl-7-(3-phenyl-prop-1-ynyl)-4*H*-[1,2,4]triazolo[4,3-*a*] quinazolin-5-one

To a suspension of 1.5 g (3.53 mmol) of compound obtained in Step 1 of Preparation C in 12 ml of DMF were added, under inert atmosphere of nitrogen, 0.574 g (4.94 mmol) of 3-phenylprop-1-yne, 1.45 g (14.4 mmol) of triethylamine and 0.1 g of dichlorobis (triphenylphosphin)palladium (II). The reaction mixture was then stirred and heated at 50°C for 5 hours. After cooling at room temperature, H_2O was added and the mixture extracted several times with AcOEt. The organic phase was washed with water and brine and then dried (Na_2SO_4) and concentrated, leaving 1.5 g of crude solid that was chromatographied on a silica column (CH_2Cl_2/CH_3OH 98.5/1.5 v/v) to afford 0.25 g (yield : 18%) of an off-white solid pure in TLC. A sample was purified by recrystallization in methanol.

Mp = 238°C

N.M.R .DMSO ^1H δ (ppm): 3.85 (s, 2H); 5.55 (s, 2H); 7.25-7.45 (m, 8H); 7.6 (d, 1H); 7.65-7.75 (m, 2H); 7.85 (d, 1H); 8.5 (s, 1H); 8.7 (s, 1H).

Example 7 : 4-Benzyl-7-[(4-methoxyphenyl)-prop-1-ynyl]-4*H*-[1,2,4]-triazolo[4,3-*a*] quinazolin-5-one

The compound was obtained according to the procedure described in Example 6 using the same substrate (Preparation C, Step 1) and 0.48 g of 3-(4-methoxyphenyl)-prop-1-yne. The crude product was purified by chromatography on a silica column (CH_2Cl_2/CH_3OH 98/2 v/v). A treatment of the resultant solid with boiling AcOEt gave 0.15 g (yield : 15%) of an off-white solid pure in TLC.

Mp = 267°C

N.M.R: $CDCl_3$ ^1H δ (ppm): 3.8 (s, 2H); 3.8 (s, 3H); 5.5 (s, 2H); 6.9 (d, 2H); 7.2-7.35 (m, 5H); 7.6 (d, 1H); 7.68 (d, 2H); 7.8 (d, 1H); 8.4 (s, 1H); 8.7 (s, 1H).

Example 8 : Methyl 4-{7-[3-(4-methoxy-phenyl)-prop-1-ynyl]-5-oxo-5*H*-[1,2,4]triazolo[4,3-*a*]quinazolin-4-ylmethyl}-benzoate

The compound was obtained according to the procedure described in Example 6 using the compound of the Preparation C Step 3, 1.1 g of 3-(4-methoxyphenyl)prop-1-yne, and 2.72 g of N-ethyl-N,N-diisopropylamine. The crude product was purified by chromatography on a silica column (CH_2Cl_2/CH_3OH 98/2 v/v). A treatment of the resultant solid with boiling AcOEt gave 1.5 g (yield : 59%) of an off-white solid pure in TLC.

Mp = 249°C

N.M.R: $CDCl_3$ ^1H δ (ppm): 3.79 (s, 2H); 3.81 (s, 3H) ; 3.88(s, 3H) ; 5.56 (s, 2H) ; 6.89 (d, 2H) ; 7.30 (d, 2H) ; 7.60 (d, 1H) ; 7.70 (d, 2H) ; 7.82 (d, 1H) ; 7.97 (d, 2H) ; 8.44 (s, 1H) ; 8.7 (s, 1H).

Example 9 : 4-[5-Oxo-7-(3-phenyl-prop-1-ynyl)-5*H*-[1,2,4]triazolo[4,3-*a*]quinazolin-4-ylmethyl]-benzoic acid

The compound was obtained according to the procedure described in Example 6 using the compound of the Preparation D (0.195 g), 0.067 g of 3-phenylprop-1-yne, and 0.215 g of N-ethyl-N,N-diisopropylamine. The crude product was purified by chromatography on a silica column (CH_2Cl_2/CH_3OH 90/10 then 85/15 v/v) to afford 0.14 g (yield : 77%) of an off-white solid pure in TLC corresponding to the desired product.

Mp = 262°C

N.M.R: DMSO ^1H δ (ppm): 3.96 (s, 2H); 5.42 (s, 2H); 7.27 (t, 1H); 7.37 (t, 2H); 7.44 (d, 2H); 7.52 (d, 2H); 7.87 (d, 2H); 8.02 (d, 1H); 8.18-8.22 (m, 2H); 9.53 (s, 1H); 12.5-13.2 (m, 1H).

Example 10 : 4-(1-Methyl-2,4-dioxo-6-(2-phenylethynyl)-1,4-dihydro-2H-quinazolin-3-ylmethyl)-benzoic acid

The compound was obtained according to the procedure described in Example 5 using the compound of the Preparation A Step 4 (0.59 g, 1.35 mmol), 0.193 g (1.89 mmol) of 1-phenyleth-1-yne, 0.050 g of dichlorobis(triphenylphosphine)palladium, a catalytic amount of CuI and 0.700 g (5.4 mmol) of N-ethyl-N,N-diisopropylamine. The crude

product was purified by crystallization in dichloromethane provided 0.55 g (yield : 100%) of an off-white solid pure in TLC.

Mp = 260°C

N.M.R: DMSO ^1H δ (ppm): 3.55 (s, 3H) ; 5.21 (s, 2H) ; 7.36-7.50 (m, 5H) ; 7.50-7.65 (m, 3H) ; 7.82-7.99 (m, 3H) ; 8.16 (s, 1H) ; 12.7-13.1 (m, 1H).

PHARMACOLOGICAL STUDIES OF COMPOUNDS OF THE INVENTION

Example 11 : Evaluation of the in vitro activity of the MMP-13 inhibitor compounds according to the invention.

The inhibitory activity of the compounds of formula (I) according to the invention with respect to matrix metalloprotease-13 is evaluated by testing the ability of the compounds of the invention to inhibit the proteolysis of a peptide substrate with MMP-13.

The peptide substrate used in the test is the following peptide: Ac-Pro-Leu-Gly-thioester-Leu-Leu-Gly-OEt.

The inhibitory activity of a compound of formula (I) according to the invention is expressed as the IC_{50} value, which is the concentration of inhibitor for which an inhibition of 50% of the activity of the matrix metalloprotease under consideration is observed.

To carry out this test, a reaction medium of 100 µl volume is prepared, containing: 50 mM of HEPES buffer, 10 mM of $CaCl_2$ and 1 mM of 5,5'-dithiobis-(2-nitrobenzoic acid) (DTNB), and 100 µM of substrate, the pH being adjusted to 7.0.

Increasing concentrations of the inhibitory compound present in a 2.0% DMSO solution and 2.5 nM of the catalytic domain of human MMP-13 are added to the test samples.

The concentrations of inhibitors present in the test samples range from 100 µM to 0.5 nM.

The measurement of the proteolysis of the substrate peptide is monitored by measuring the absorbence at 405 nm using a spectrophotometer for reading microplates, at the laboratory temperature, the measurements being carried out continuously for 10 to 15 minutes.

The IC_{50} values are calculated from a curve in which the percentage of the catalytic activity relative to the control is represented on the X-axis and the concentration of inhibitor is represented on the Y-axis.

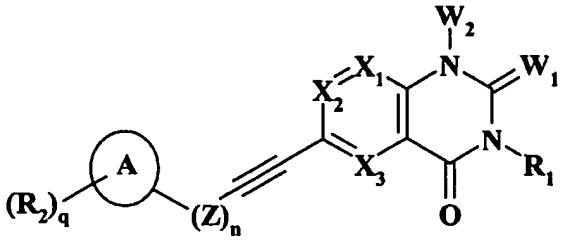
The IC_{50} values on MMP-13 of the compounds of Examples 1 to 10 are all below 1 μM.

The test described above for the inhibition of MMP-13 was also adapted and used to determine the ability of the compounds of formula (I) to inhibit the matrix metalloproteases MMP-1, MMP-2, MMP-3, MMP-7, MMP-9, MMP-12 and MMP-14.

5 The results obtained show that the compounds according to the invention generally have IC_{50} values for MMP-13 which are about 100 times lower than the IC_{50} values for the same compounds with respect to the other matrix metalloproteases tested.

CLAIMS

1- A compound selected from those of formula (I) :



(I)

wherein :

W_1 represents an oxygen atom, a sulfur atom, or a $-NR_3$ group in which R_3 represents hydrogen atom, (C_1-C_6)alkyl, hydroxyl or cyano,

W_2 represents a group selected from :

- hydrogen atom, trifluoromethyl, amino, mono(C_1-C_{10})alkylamino, di(C_1-C_{10})alkylamino, each alkyl moiety being identical or different,
- (C_1-C_6)alkyl, (C_3-C_6)alkenyl, (C_3-C_6)alkynyl, (C_5-C_{10})aryl, (C_5-C_{10})aryl(C_1-C_{10})alkyl, (C_3-C_{10})cycloalkyl(C_1-C_{10})alkyl, and the residue of an aromatic or non aromatic heterocycle comprising 5 or 6 ring members including from 1 to 4 hetero atoms selected from nitrogen, oxygen and sulfur, these groups being optionally substituted by one or more groups, which may be identical or different, selected from halogen, amino, mono(C_1-C_{10})alkylamino, di(C_1-C_{10})alkylamino, each alkyl moiety being identical or different, cyano, trihalogeno(C_1-C_6)alkyl, (C_1-C_6)acyl, $-C(=O)OR_4$, $-OR_4$ and $-SR_4$, R_4 representing a hydrogen atom or a (C_1-C_6)alkyl group,

or W_1 and W_2 form together a group of formula $N-X_4=W_3$ (in which the nitrogen atom is bonded on the place of the group W_1 and the group W_3 is bonded on the place of the group W_2) wherein:

- W_3 represents a nitrogen atom or a group $-CR_5$ in which R_5 is selected from :
  - a hydrogen atom,

- $-OR_6$, $-SR_6$ in which R_6 is selected from hydrogen, (C_1-C_6)alkyl and (C_5-C_{10})aryl(C_1-C_{10})alkyl;
- (C_1-C_6)alkyl, (C_3-C_{10})cycloalkyl, the residue of a saturated heterocycle comprising from 3 to 8 ring members including one hetero atom selected from oxygen, sulfur and nitrogen, (C_5-C_{10})aryl, (C_5-C_{10})heteroaryl comprising from 1 to 4 hetero atoms selected from oxygen, sulfur and nitrogen, and (C_5-C_{10})aryl(C_1-C_{10})alkyl, these groups being optionally substituted by $-(CH_2)_p-OH$ or $-(CH_2)_p-NH_2$, wherein p is an integer from 0 to 4 inclusive,

- X_4 represents a nitrogen atom or a group $-CR_7$ in which R_7 is selected from hydrogen, $-NR_8R_9$, $-OR_8$, $-SR_8$, (C_1-C_6)alkyl, (C_3-C_{10})cycloalkyl, the residue of a saturated heterocycle comprising from 3 to 8 ring members including one hetero atom selected from oxygen, sulfur and nitrogen, (C_5-C_{10})aryl, (C_5-C_{10})heteroaryl comprising from 1 to 4 hetero atoms selected from oxygen, sulfur and nitrogen, and (C_5-C_{10})aryl(C_1-C_{10})alkyl, these groups being optionally substituted by $-(CH_2)_p-OH$ or $-(CH_2)_p-NH_2$ wherein p is an integer from 0 to 4 inclusive,
  and in which R_8 and R_9, identical or different, are selected from hydrogen, (C_1-C_6)alkyl and (C_5-C_{10})aryl(C_1-C_{10})alkyl,

X_1, X_2 and X_3 represent, independently of each other, a nitrogen atom or a carbon atom, the said carbon atom being unsubstituted or substituted with a group selected from :

- (C_1-C_6)alkyl, hydroxyl, (C_1-C_6)alkoxy, halogen, trifluoromethyl, cyano, nitro,
- $-S(O)_{n1}R_4$ wherein n_1 represents an integer from 0 to 2 inclusive and R_4 represents an hydrogen atom or a (C_1-C_6)alkyl group,
- and $-NR_{10}R_{11}$ wherein R_{10} and R_{11}, which may be identical or different, represent a group selected from hydrogen atom, (C_1-C_6)alkyl, and (C_5-C_{10})aryl(C_1-C_{10})alkyl, or R_{10} and R_{11} form together with the nitrogen atom to which there are bonded, a 5- or 6-ring members which can optionally contain a second hetero atom selected from nitrogen and oxygen,

with the proviso that not more than two of the groups X_1, X_2 and X_3 simultaneously represent a nitrogen atom,

n is an integer from 0 to 8 inclusive,

Z represents $-CR_{12}R_{13}$, wherein R_{12} and R_{13} independently of each other, represent a group selected from hydrogen, (C_1-C_6)alkyl, trihalogeno(C_1-C_6)alkyl, halogen, amino, mono(C_1-C_6)alkylamino, di(C_1-C_6)alkylamino in which each alkyl moiety is identical or different, $-OR_4$, $-SR_4$, and $-C(=O)OR_4$, R_4 being as defined hereinbefore, or $-CR_{12}R_{13}$ form together a carbonyl group, and

-when n is greater than or equal to 2, the hydrocarbon chain Z optionally contains one or more multiple bonds,

-and/or one of the carbon atoms in the hydrocarbon chain Z may be replaced with an oxygen atom, a sulfur atom which is unsubstituted or substituted with one or two oxygen, or a nitrogen atom which is unsubstituted or substituted with a (C_1-C_6)alkyl,

A represents the residue of an aromatic or non-aromatic 5- or 6-membered monocycle comprising from 0 to 4 hetero atoms selected from nitrogen, oxygen and sulfur, or a bicycle composed of two aromatic or non-aromatic 5- or 6-membered rings, which may be identical or different, comprising from 0 to 4 hetero atoms selected from nitrogen, oxygen and sulfur,

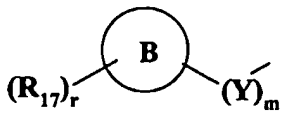
the group(s) R_2, which may be identical or different, are selected from hydrogen, (C_1-C_6)alkyl, halogen, cyano, nitro, trihalogeno(C_1-C_6)alkyl, $-NR_{10}R_{11}$, $-OR_{14}$, $-SR_{14}$, $-SOR_{14}$, $-SO_2R_{14}$, (C_1-C_6)acyl, $-(CH_2)_kNR_{10}R_{11}$, $-X_5(CH_2)_kNR_{10}R_{11}$, $-(CH_2)_kSO_2NR_{14}R_{15}$, $-X_5(CH_2)_kC(=O)OR_{14}$, $-(CH_2)_kC(=O)OR_{14}$, $-X_5(CH_2)_kC(=O)NR_{14}R_{15}$, $-(CH_2)_kC(=O)NR_{14}R_{15}$ and $-X_6-R_{16}$ in which :

- X_5 represents an oxygen atom, a sulfur atom, a -NH group, or a $-N(C_1-C_6)$alkyl group,
- k is an integer from 0 and 3 inclusive,
- R_{10} and R_{11} are as defined hereinbefore,
- R_{14} and R_{15}, identical or different, represent hydrogen or (C_1-C_6)alkyl,
- X_6 represents a single bond, $-CH_2-$, an oxygen atom or a sulfur atom which is unsubstituted or substituted with one or two oxygen atoms,
- R_{16} represents the residue of an aromatic or non-aromatic, heterocyclic or non-heterocyclic, 5- or 6-membered ring which is unsubstituted or substituted with one or

more groups, which may be identical or different, selected from (C_1-C_6)alkyl, halogen, trihalogeno(C_1-C_6)alkyl, hydroxyl, (C_1-C_6)alkoxy, mercapto, (C_1-C_6)alkylthio, amino, mono(C_1-C_6)alkylamino, di(C_1-C_6)alkylamino each alkyl moiety being identical or different, and when the ring is heterocyclic, it comprises from 1 to 4 hetero atoms selected from nitrogen, oxygen and sulfur,

q is an integer from 0 to 7 inclusive,

R_1 represents a group selected from hydrogen, (C_1-C_6)alkyl, (C_3-C_6)alkenyl, and (C_3-C_6)alkynyl, the groups alkyl, alkenyl and alkynyl being optionally substituted with one or more groups, which may be identical or different, selected from amino, mono(C_1-C_6)alkylamino, di(C_1-C_6)alkylamino in which each alkyl moiety is identical or different, (C_1-C_6)alkyl, cyano, trihalogeno(C_1-C_6)alkyl, -C(=O)OR_4, -OR_4, -SR_4, in which R_4 is as defined above, and the group of formula :



in which:

- m is an integer from 0 to 8 inclusive,
- Y represents -$CR_{18}R_{19}$, wherein R_{18} and R_{19} independently of each other, represent a group selected from hydrogen, (C_1-C_6)alkyl, phenyl, trihalogeno(C_1-C_6)alkyl, halogen, amino, mono(C_1-C_6)alkylamino, di(C_1-C_6)alkylamino in which each alkyl moiety is identical or different, -OR_4, -SR_4 or -C(=O)OR_4 wherein R_4 is as defined above, and
  - when m is greater than or equal to 2, the hydrocarbon chain Y optionally contains one or more multiple bonds,
  - and/or one of the carbon atoms in the hydrocarbon chain Y may be replaced with an oxygen atom, a sulfur atom which is unsubstituted or substituted with one or two oxygen, or a nitrogen atom which is unsubstituted or substituted with (C_1-C_6)alkyl,
- B represents a group selected from the residue of an aromatic or non-aromatic, 5- or 6-membered monocycle comprising from 0 to 4 hetero atoms selected from nitrogen, oxygen and sulfur, and a bicycle, composed of two aromatic or non-aromatic, 5- or 6-

membered rings, which may be identical or different, comprising from 0 to 4 hetero atoms selected from nitrogen, oxygen and sulfur,

- r is an integer from 0 to 7 inclusive,
- the group(s) R_{17} which may be identical or different are selected from hydrogen, (C_1-C_6)alkyl, halogen, cyano, nitro, trihalogeno(C_1-C_6)alkyl, $-NR_{10}R_{11}$, $-OR_{14}$, $-SR_{14}$, $-SOR_{14}$, $-SO_2R_{14}$, (C_1-C_6)acyl, $-(CH_2)_kNR_{10}R_{11}$, $-X_5(CH_2)_kNR_{10}R_{11}$, $-(CH_2)_kSO_2NR_{14}R_{15}$, $-X_5(CH_2)_kC(=O)OR_{14}$, $-(CH_2)_kC(=O)OR_{14}$, $-X_5(CH_2)_kC(=O)NR_{14}R_{15}$, $-(CH_2)_kC(=O)NR_{14}R_{15}$ and the group of formula $-X_6-R_{16}$ in which X_5, k, R_{10}, R_{11}, R_{14}, R_{15}, X_6 and R_{16} are as defined hereinbefore, and

optionally, its optical isomers , N-oxides, and addition salts thereof with a pharmaceutically-acceptable acid or base.

2- A compound according to claim 1, wherein :

W_1 represents an oxygen atom, a sulfur atom, or a $-NR_3$ group in which R_3 represents hydrogen atom, (C_1-C_6)alkyl, hydroxyl or cyano,

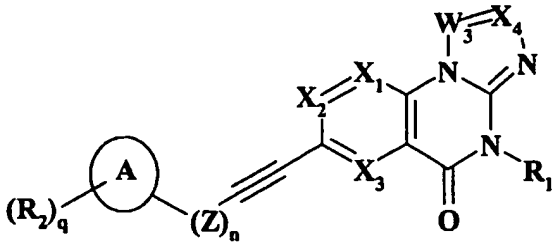
W_2 represents a group selected from :

- hydrogen atom, trifluoromethyl, amino, mono(C_1-C_{10})alkylamino, di(C_1-C_{10})alkylamino, each alkyl moiety being identical or different,
- (C_1-C_6)alkyl, (C_3-C_6)alkenyl, (C_3-C_6)alkynyl, (C_5-C_{10})aryl, (C_5-C_{10})aryl(C_1-C_{10})alkyl, (C_3-C_{10})cycloalkyl(C_1-C_{10})alkyl, and the residue of an aromatic or non aromatic heterocycle comprising 5 or 6 ring members including from 1 to 4 hetero atoms selected from nitrogen, oxygen and sulfur, these groups being optionally substituted by one or more groups, which may be identical or different, selected from halogen, amino, mono(C_1-C_{10})alkylamino, di(C_1-C_{10})alkylamino, each alkyl moiety being identical or different, cyano, trihalogeno(C_1-C_6)alkyl, (C_1-C_6)acyl, $-C(=O)OR_4$, $-OR_4$ and $-SR_4$, R_4 representing a hydrogen atom or a (C_1-C_6)alkyl group,

and X_1, X_2, X_3, R_1, R_2, A, Z, n and q are as defined in formula (I),

optionally, its optical isomers , N-oxides, and addition salts thereof with a pharmaceutically-acceptable acid or base.

3- A compound according to claim 1 in which it represents a compounds of formula (IA) :



(I/A)

wherein

W_3 represents a nitrogen atom or a group $-CR_5$ in which R_5 is selected from :

- a hydrogen atom,
- $-OR_6$, $-SR_6$ in which R_6 is selected from hydrogen, (C_1-C_6)alkyl and (C_5-C_{10})aryl(C_1-C_{10})alkyl;
- (C_1-C_6)alkyl, (C_3-C_{10})cycloalkyl, the residue of a saturated heterocycle comprising from 3 to 8 ring members including one hetero atom selected from oxygen, sulfur and nitrogen, (C_5-C_{10})aryl, (C_5-C_{10})heteroaryl comprising from 1 to 4 hetero atoms selected from oxygen, sulfur and nitrogen, and (C_5-C_{10})aryl(C_1-C_{10})alkyl, these groups being optionally substituted by $-(CH_2)_p-OH$ or $-(CH_2)_p-NH_2$, wherein p is an integer from 0 to 4 inclusive,

X_4 represents a nitrogen atom or a group $-CR_7$ in which R_7 is selected from hydrogen, $-NR_8R_9$, $-OR_8$, $-SR_8$, (C_1-C_6)alkyl, (C_3-C_{10})cycloalkyl, the residue of a saturated heterocycle comprising from 3 to 8 ring members including one hetero atom selected from oxygen, sulfur and nitrogen, (C_5-C_{10})aryl, (C_5-C_{10})heteroaryl comprising from 1 to 4 hetero atoms selected from oxygen, sulfur and nitrogen, and (C_5-C_{10})aryl(C_1-C_{10})alkyl, these groups being optionally substituted by $-(CH_2)_p-OH$ or $-(CH_2)_p-NH_2$ wherein p is an integer from 0 to 4 inclusive,

and in which R_8 and R_9, identical or different, are selected from hydrogen, (C_1-C_6)alkyl and (C_5-C_{10})aryl(C_1-C_{10})alkyl,

and X_1, X_2, X_3, R_1, R_2, A, Z, n and q are as defined hereinbefore.

optionally, its optical isomers , N-oxides, and addition salts thereof with a pharmaceutically-acceptable acid or base.

4- A compound according to claim 1 wherein :

W_2 represents a group selected from hydrogen atom, $(C_1$-$C_6)$alkyl, $(C_5$-$C_{10})$aryl$(C_1$-$C_6)$alkyl and $(C_3$-$C_6)$cycloalkyl$(C_1$-$C_6)$alkyl,

W_1 represents an oxygen atom or a sulfur atom,

X_1 represents a -CH group,

X_2 represents a -CH group or a nitrogen atom,

X_3 represents a -CH group,

and R_1, R_2, A, Z, n and q are as defined in formula (I),

optionally, its optical isomers , N-oxides, and addition salts thereof with a pharmaceutically-acceptable acid or base.

5- A compound according to claim 1 wherein :

W_2 represents a group selected from hydrogen atom, amino, mono$(C_1$-$C_{10})$alkylamino, di$(C_1$-$C_{10})$alkylamino, each alkyl moiety being identical or different, $(C_1$-$C_6)$alkyl, $(C_3$-$C_6)$alkenyl, $(C_3$-$C_6)$alkynyl, $(C_5$-$C_{10})$aryl, $(C_5$-$C_{10})$aryl$(C_1$-$C_6)$alkyl, and $(C_3$-$C_6)$cycloalkyl$(C_1$-$C_6)$alkyl,

W_1 represents an oxygen atom or a sulfur atom,

X_1 represents a nitrogen atom or a -CH group

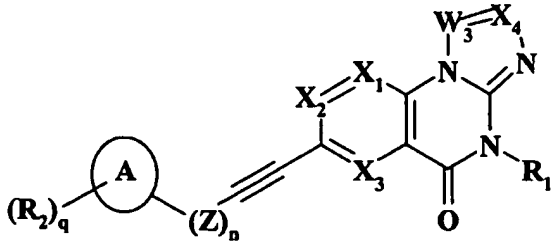
X_2 represents a -CH group,

X_3 represents a -CH group,

and R_1, R_2, A, Z, n and q are as defined in formula (I),

optionally, its optical isomers , N-oxides, and addition salts thereof with a pharmaceutically-acceptable acid or base.

6- A compound according to claim 3 wherein it represents a compound of formula (IA) :



(I/A)

in which:

W_3 represents -CR_5 wherein R_5 represents a hydrogen atom or a methyl group,

X_4 represents a nitrogen atom or $-CR_7$ wherein R_7 represents a hydrogen atom or a methyl group,

n is an integer from 1 to 4 inclusive,

and X_1, X_2, X_3, R_1, R_2, A, Z and q are as defined in the formula (I),

optionally, its optical isomers , N-oxides, and addition salts thereof with a pharmaceutically-acceptable acid or base.

7- A compound according to claim 1 wherein :

A represents a group selected from phenyl, pyridinyl, thienyl, imidazolyl, furyl, benzodioxolyl, benzodioxinyl, benzothienyl, benzofuryl, benzo-1,2,5-thiadiazolyl, benzo-1,2,5-oxadiazolyl or indolyl,

q is an integer from 0 to 4 inclusive,

the group(s) R_2,which may be identical or different, are selected from hydrogen, $(C_1$-$C_6)$alkyl, halogen, cyano, nitro, trihalogeno$(C_1$-$C_6)$alkyl, $-NR_{14}R_{15}$, $-OR_{14}$, $-SO_2R_{14}$, $-(CH_2)_kSO_2NR_{14}R_{15}$, $-X_5(CH_2)_kC(=O)OR_{14}$, $-(CH_2)_kC(=O)OR_{14}$, $-X_5(CH_2)_kC(=O)NR_{14}R_{15}$, $-(CH_2)_kC(=O)NR_{14}R_{15}$ and $-X_6$-R_{16} in which :

- X_5 represents an oxygen atom, a sulfur atom, or a -NH group,
- k is an integer from 0 and 3 inclusive,
- R_{14} and R_{15} identical or different represent hydrogen or $(C_1$-$C_6)$alkyl,
- X_6 represents an oxygen atom,
- R_{16} represents a phenyl group which is unsubstituted or substituted with one or more groups, which may be identical or different, selected from $(C_1$-$C_6)$alkyl, halogen, and hydroxyl,

and W_1, W_2, X_1, X_2, X_3, R_1, Z and n are as defined in formula (I),

optionally, its optical isomers , N-oxides, and addition salts thereof with a pharmaceutically-acceptable acid or base.

8- A compound according to claim 1 wherein :

A represents a group selected from phenyl, pyridinyl, thienyl, imidazolyl, furyl, and benzodioxolyl,

q is an integer from 0 to 4 inclusive,

the group(s) R_2, which may be identical or different, are selected from hydrogen, $(C_1\text{-}C_6)$alkyl, halogen, cyano, nitro, trihalogeno$(C_1\text{-}C_6)$alkyl, $-NR_{14}R_{15}$, $-OR_{14}$, $-SO_2R_{14}$, $-(CH_2)_kSO_2NR_{14}R_{15}$, $-X_5(CH_2)_kC(=O)OR_{14}$, $-(CH_2)_kC(=O)OR_{14}$, $-X_5(CH_2)_kC(=O)NR_{14}R_{15}$, and $-(CH_2)_kC(=O)NR_{14}R_{15}$ in which :

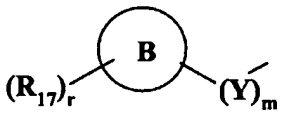
- X_5 represents an oxygen atom, a sulfur atom, or a -NH group,
- k is an integer from 0 and 3 inclusive,
- R_{14} and R_{15}, identical or different, represent hydrogen or $(C_1\text{-}C_6)$alkyl,

and W_1, W_2, X_1, X_2, X_3, R_1, Z and n are as defined in formula (I),

optionally, its optical isomers , N-oxides, and addition salts thereof with a pharmaceutically-acceptable acid or base.

9- A compound according to claim 1 wherein :

R_1 represents hydrogen, $(C_1\text{-}C_6)$alkyl or the group of formula :



in which:

- m is an integer from 0 to 3 inclusive,
- Y represents $-CR_{18}R_{19}$, wherein R_{18} and R_{19} independently of each other, represent a group selected from hydrogen, $(C_1\text{-}C_6)$alkyl, and phenyl,
  - and when m is greater than or equal to 2, the hydrocarbon chain Y optionally contains one multiple bonds,
  - and/or one of the carbon atoms in the hydrocarbon chain Y may be replaced with an oxygen atom, a sulfur atom which is unsubstituted or substituted with one or two oxygen, or a nitrogen atom which is unsubstituted,
- B represents a group selected from phenyl, pyridinyl, thienyl, imidazolyl, furyl, benzodioxolyl, benzodioxinyl, benzothienyl, benzofuryl, benzo-1,2,5-thiadiazolyl, benzo-1,2,5-oxadiazolyl, naphtyl and indolyl,
- r is an integer from 0 to 3 inclusive,

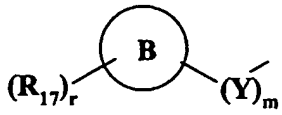
- the group(s) R_{17} which may be identical or different are selected from hydrogen, (C_1-C_6)alkyl, halogen, cyano, nitro, trihalogeno(C_1-C_6)alkyl, $-NR_{14}R_{15}$, $-OR_{14}$, $-SO_2R_{14}$, $(CH_2)_kSO_2NR_{14}R_{15}$, $X_5(CH_2)_kC(=O)OR_{14}$, $(CH_2)_kC(=O)OR_{14}$, $X_5(CH_2)_kC(=O)NR_{14}R_{15}$, $-(CH_2)_kC(=O)NR_{14}R_{15}$ wherein :
  - k is an integer from 0 to 3 inclusive,
  - X_5 represents an oxygen atom, a sulfur atom, or a group -NH,
  - R_{14} and R_{15}, identical or different, represent a hydrogen atom or a (C_1-C_6)alkyl group,

and W_1, W_2, X_1, X_2, X_3, R_2, Z, n and q are as defined in formula (I),

optionally, its optical isomers , N-oxides, and addition salts thereof with a pharmaceutically-acceptable acid or base.

10- A compound according to claim 1 wherein :

R_1 represents a group of formula :



in which:

- m is an integer from 0 to 3 inclusive,
- Y represents $-CR_{18}R_{19}$, wherein R_{18} and R_{19} independently of each other, represent a group selected from hydrogen and methyl,
  - and when m is greater than or equal to 2, the hydrocarbon chain Y optionally contains one double bonds,
  - and/or one of the carbon atoms in the hydrocarbon chain Y may be replaced with an oxygen atom, a sulfur atom which is unsubstituted or substituted with one or two oxygen, or a nitrogen atom which is unsubstituted,
- B represents a group selected from phenyl, pyridinyl, thienyl, imidazolyl, furyl, and benzodioxolyl,
- r is an integer from 0 to 3 inclusive,
- the group(s) R_{17} which may be identical or different are selected from hydrogen, (C_1-C_6)alkyl, halogen, cyano, nitro, trihalogeno(C_1-C_6)alkyl, $-NR_{14}R_{15}$, $-OR_{14}$, $-SO_2R_{14}$,

$(CH_2)_kSO_2NR_{14}R_{15}$, $X_5(CH_2)_kC(=O)OR_{14}$, $(CH_2)_kC(=O)OR_{14}$, $X_5(CH_2)_kC(=O)NR_{14}R_{15}$, $-(CH_2)_kC(=O)NR_{14}R_{15}$ wherein :

- k is an integer from 0 to 3inclusive,
- X_5 represents an oxygen atom, a sulfur atom, or a group –NH,
- R_{14} and R_{15}, identical or different, represent a hydrogen atom or a (C_1-C_6)alkyl group,

and W_1, W_2, X_1, X_2, X_3, R_2, Z, n and q are as defined in formula (I),
optionally, its optical isomers , N-oxides, and addition salts thereof with a pharmaceutically-acceptable acid or base.

11- A compound according to claim 1 wherein n is equal to one, optionally, its optical isomers, N-oxides, and addition salts thereof with a pharmaceutically-acceptable acid or base.

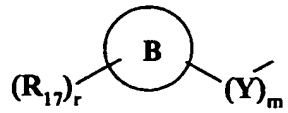
12- A compound according to claim 1 wherein Z represents a group $-CR_{12}R_{13}$ in which R_{12} and R_{13} represent each a hydrogen atom, optionally, its optical isomers, N-oxides, and addition salts thereof with a pharmaceutically-acceptable acid or base.

13- A compound according to claim 1 wherein A represents a 5- to 6- membered aromatic monocycle optionally substituted by one or more groups R_2 as defined in the compound of formula (I), optionally, its optical isomers, N-oxides, and addition salts thereof with a pharmaceutically-acceptable acid or base.

14- A compound according to claim 13 wherein A represents a phenyl group optionally substituted by one group R_2 as defined in the compound of the formula (I), optionally, its optical isomers, N-oxides, and addition salts thereof with a pharmaceutically-acceptable acid or base.

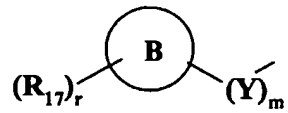
15- A compound according to claim 13 wherein A represents a phenyl group and R_2 represents a methoxy group, optionally, its optical isomers, N-oxides, and addition salts thereof with a pharmaceutically-acceptable acid or base.

16- A compound according to claim 2 wherein W_2 represents an oxygen atom, W_1 represent a linear or branched (C_1-C_6)alkyl group and R_1 represent a group of formula :



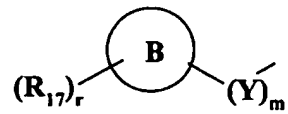
in which Y, B, R_{17}, m and r are as defined in the compound of formula (I), optionally, its optical isomers, N-oxides, and addition salts thereof with a pharmaceutically-acceptable acid or base.

17- A compound according to claim 16 wherein R_1 represent a group of formula :



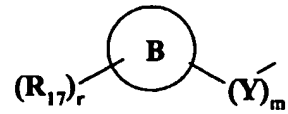
in which m is equal to one, Y represents a methylene group, B represents a phenyl group which is optionally substituted by one group R_{17} which represents a group $(CH_2)_k$-C(=O)OR_{14} in which k and R_{14} are as defined in the compound of formula (I), optionally, its optical isomers, N-oxides, and addition salts thereof with a pharmaceutically-acceptable acid or base.

18- A compound according to claim 3 wherein W_3 represents a group -CR_5 in which R_5 is a hydrogen atom, X_4 represents a nitrogen atom and R_1 represents a group of formula :



in which Y, B, R_{17}, m and r are as defined in the compound of formula (IA), optionally, its optical isomers, N-oxides, and addition salts thereof with a pharmaceutically-acceptable acid or base.

19- A compound according to claim 18 wherein R_1 represent a group of formula :



in which m is equal to one, Y represents a methylene group, B represents a phenyl group which is optionally substituted by one group R_{17} which represents a group

-$(CH_2)_k$-C(=O)OR_{14} in which k and R_{14} are as defined in the compound of formula (IA), optionally, its optical isomers, N-oxides, and addition salts thereof with a pharmaceutically-acceptable acid or base.

20- A compound according to claim 1, which is selected from :

Methyl 4-{6-[3-(4-methoxyphenyl)-prop-1-ynyl]-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl}-benzoate,

4-[1-Methyl-2,4-dioxo-6-(3-phenyl-prop-1-ynyl)-1,4-dihydro-2*H*-quinazolin-3-ylmethyl]-benzoic acid,

4-{6-[3-(4-Methoxy-phenyl)-prop-1-ynyl]-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-ylmethyl}-benzoic acid,

4-[1-Methyl-2,4-dioxo-6-(3-phenyl-prop-1-ynyl)-1,4-dihydro-2*H*-pyrido[3,4-*d*]pyrimidin-3-ylmethyl]-benzoic acid,

4-{6-[3-(4-Methoxy-phenyl)-prop-1-ynyl]-1-methyl-2,4-dioxo-1,4-dihydro-2*H*-pyrido[3,4-*d*]pyrimidin-3-ylmethyl}-benzoic acid,

4-Benzyl-7-(3-phenyl-prop-1-ynyl)-4*H*-[1,2,4]triazolo[4,3-*a*]quinazolin-5-one,

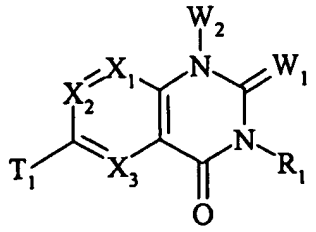
4-Benzyl-7-[(4-methoxyphenyl)-prop-1-ynyl]-4*H*-[1,2,4]-triazolo[4,3-*a*] quinazolin-5-one,

Methyl 4-{7-[3-(4-methoxy-phenyl)-prop-1-ynyl]-5-oxo-5*H*-[1,2,4]triazolo[4,3-*a*] quinazolin-4-ylmethyl}-benzoate,

4-[5-Oxo-7-(3-phenyl-prop-1-ynyl)-5*H*-[1,2,4]triazolo[4,3-*a*]quinazolin-4-ylmethyl]-benzoic acid,

and 4-(1-Methyl-2,4-dioxo-6-(2-phenylethynyl)-1,4-dihydro-2H-quinazolin-3-ylmethyl)-benzoic acid.

21- A process for the preparation of compounds according to claim 1 in which uses as starting material a compound of formula (II):

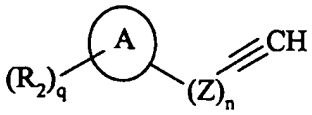


(II)

in which R_1, W_1, W_2, X_1, X_2 and X_3 have the same definitions as the compounds of formula (I), and T_1 represents a group selected from hydrogen, halogen, mesylate, triflate, formyl, acetyl, and ester,

compound of formula (II) which is treated :

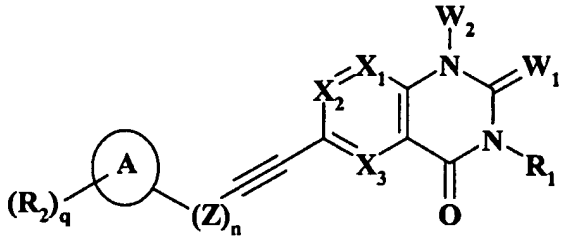
❖ either when T_1 represents an halogen atom, a mesylate group, or a triflate group, in the presence of a base under conditions of palladium-catalyzed alkynylation with a compound of formula (III):



(III)

in which A, Z, R_2, q and n are as defined for the compounds of formula (I),

to yield the compounds of formula (I),

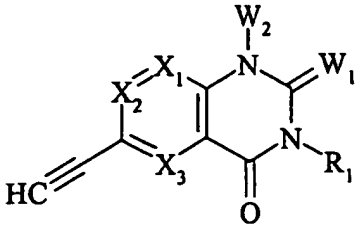


(I)

❖ or when T_1 represents an hydrogen atom, with iodine to yield *in situ* the corresponding iodide intermediate, which is treated directly without isolation or purification, with a compound of formula (III) as described hereinbefore, under conditions of palladium-catalyzed alkynylation in the presence of a base,

to yield the compounds of formula (I),

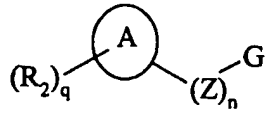
❖ or when T_1 represents an acetyl group, first with lithium diisopropylamine at -78°C in an inert solvent to provide an enolate, second with diethyl chlorophosphate and subsequently with lithium diisopropylamine, to yield a compound of formula (IV):



(IV)

in which R_1, W_1, W_2, X_1, X_2 and X_3 are as defined hereinbefore,

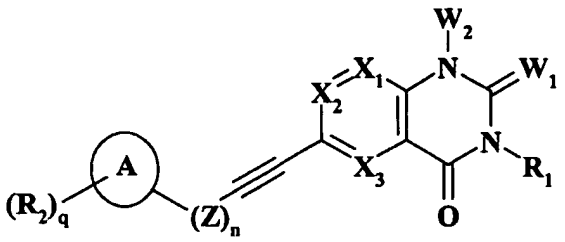
and condensing the compound of formula (IV), in the presence of triphenylphosphin and $PdCl_2(PPh_3)_2$, under basic conditions to a compound of formula (V):



(V)

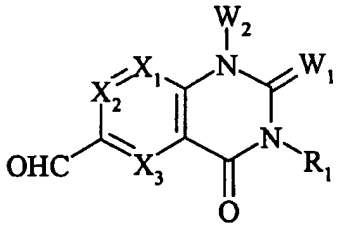
in which A, Z, R_2, q and n are as defined hereinbefore and G represents a leaving group,

to yield the compound of formula (I),



(I)

❖ or when T_1 represents an ester group, with a reductive agent, to yield the corresponding aldehyde compound of formula (VI):

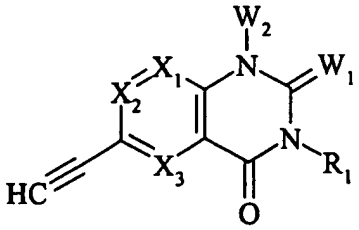


(VI)

in which R_1, W_1, W_2, X_1, X_2 and X_3 are as defined hereinbefore,

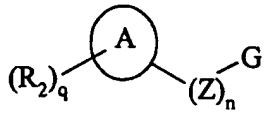
and subsequently :

- either condensing said compound of formula (VI), in basic conditions, with diazomethyl trimethyl silane or with diazomethyl diethoxy phosphonate, to yield, after basic treatment, a compound of formula (IV) as defined hereinbefore :



(IV)

and adding said compound of formula (IV) to a compound of formula (V) as described hereinbefore :

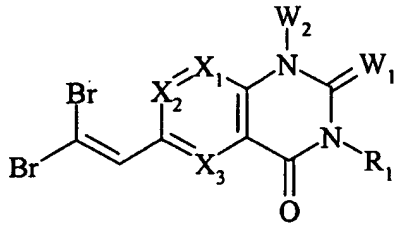


(V)

in which R_2, A, Z, q, n and G are as defined hereinbefore,

to yield the compound of formula (I),

- or reacting, said compound of formula (VI), with tetrabromomethane in the presence of triphenylphosphine in an aprotic solvent to yield a compound of formula (VII) :

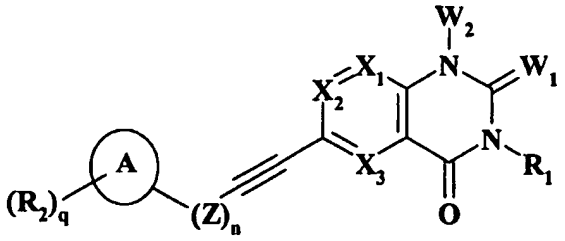


(VII)

in which R_1, W_1, W_2, X_1, X_2 and X_3 are as defined hereinbefore,

and dehalogenating said compound of formula (VII) throug treatment with a strong base in an inert solvent, or with butyllithium in presence of triphenylphosphine and zinc, to yield the compound of formula (IV) as defined hereinbefore,

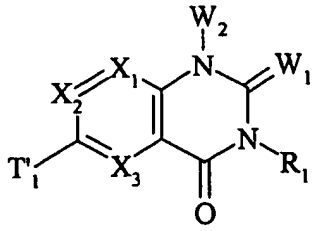
and reacting said compound of formula (IV) with a compound of formula (V) as defined in the previous step to yield a compound of a general formula (I):



(I)

which constitute the compounds of the invention, which are purified, where appropriate, according to a conventional purification technique, which are separated, where appropriate, into their different isomers according to a conventional separation technique, and which are converted, where appropriate, into addition salts thereof with a pharmaceutically-acceptable acid or base.

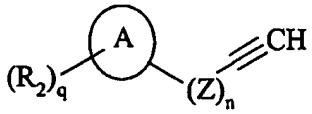
22- A process for the preparation of compounds according to claim 1 wherein it is used as starting material a compound of formula (II/A) :



(II/A)

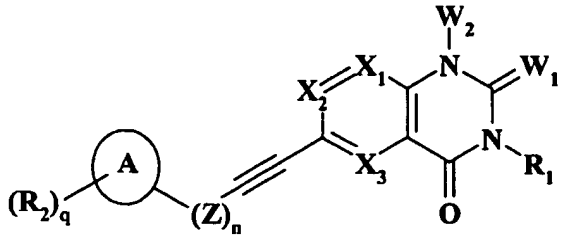
in which R_1, W_1, W_2, X_1, X_2 and X_3 have the same definitions than in the compounds of formula (I), and T'_1 represents a group selected from halogen, mesylate, and triflate,

compound of formula (II/a) which is condensed, in the presence of dichlorobis(triphenylphosphine)palladium, cupper iodide and *N,N'*-diisopropylethylamine in dimethylformamide, on a compound of formula (III):



(III)

in which A, Z, R_2, q and n are as defined in the compounds of formula (I),
to yield the compounds of formula (I),

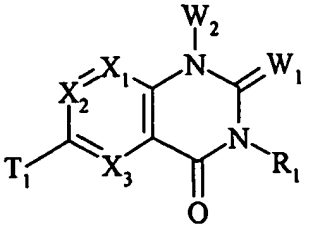


(I)

wherein W_1, W_2, X_1, X_2, X_3, R_1, R_2, A, Z, n and q are as described in claim 1.

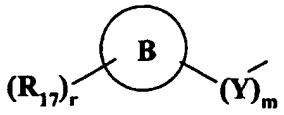
23- A process for the preparation of compounds according to claim 2 comprising the following step :

- reacting as starting material, a compound of formula (II/A) :



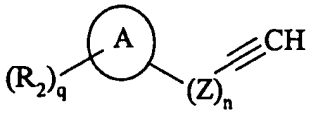
(II/A)

in which W_1 represents an oxygen atom, W_2 represents a (C_1-C_6)alkyl group, X_1 represents a -CH group, X_2 represents a nitrogen atom or a -CH group, X_3 represents a -CH group, and T_1 represent a iodine atom or a triflate group, and R_1 represents a group of formula :



in which Y represents a methylene group, m is equal to one, B represents a phenyl group, R_{17} is as defined in the compound of formula (I) and r is equal to one,

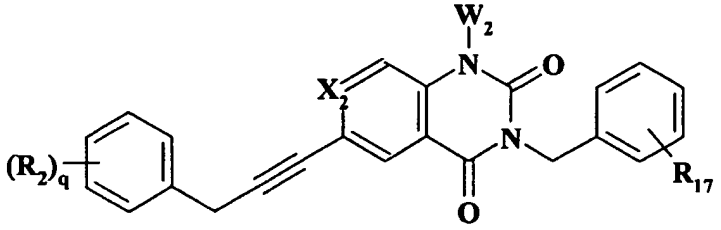
- with, as reagent, a compound of formula (III) :



(III)

in which Z represents a methylene group, n is equal to one, A is a phenyl group, q is equal to zero or one, and R_2 is as defined in the compound of formula (I),

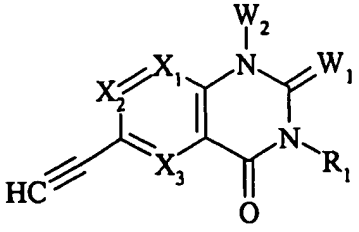
to yield a compound of formula (I/a), which constitutes a particular subgroup of the compounds of formula (I):



(I/a)

in which W_2, X_2, R_2, q and R_{17} are as defined hereinbefore.

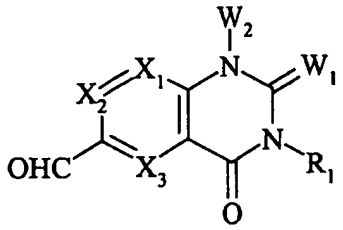
24- Intermediate compound of formula (IV) :



(IV)

wherein W_1, W_2, X_1, X_2, X_3, R_1 and R_2 are as described in claim 1.

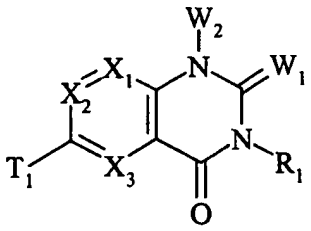
25- Intermediate compound of formula (VI) :



(VI)

wherein W_1, W_2, X_1, X_2, X_3 and R_1 are as defined in claim (I).

26- Intermediate compound of formula (II/A) :



(II/A)

wherein :

W_1 represents an oxygen atom, a sulfur atom, or a $-NR_3$ group in which R_3 represents hydrogen atom, (C_1-C_6)alkyl, hydroxyl or cyano,

W_2 represents a group selected from :

- hydrogen atom, trifluoromethyl, amino, mono(C_1-C_{10})alkylamino, di(C_1-C_{10})alkylamino, each alkyl moiety being identical or different,
- (C_1-C_6)alkyl, (C_3-C_6)alkenyl, (C_3-C_6)alkynyl, (C_5-C_{10})aryl, (C_5-C_{10})aryl(C_1-C_{10})alkyl, (C_3-C_{10})cycloalkyl(C_1-C_{10})alkyl, and the residue of an aromatic or non aromatic heterocycle comprising 5 or 6 ring members including from 1 to 4 hetero atoms selected from nitrogen, oxygen and sulfur, these groups being optionally substituted by one or more groups, which may be identical or different, selected from halogen, amino, mono(C_1-C_{10})alkylamino, di(C_1-C_{10})alkylamino, each alkyl moiety being identical or different, cyano, trihalogeno(C_1-C_6)alkyl, (C_1-C_6)acyl, $-C(=O)OR_4$, $-OR_4$ and $-SR_4$, R_4 representing a hydrogen atom or a (C_1-C_6)alkyl group,

T_1 represents a halogen atom,

and R_1, X_1, X_2, and X_3 are as defined in the compounds of formula (I).

27- A method for treating a living body afflicted with a disease where the inhibition of type -13 matrix metalloprotease is involved, comprising the step of administering to the living body an amount of a compound of claim 1 which is effective for alleviation of said conditions.

28- A method for treating a living body afflicted with a disease selected from arthritis, rheumatoid arthritis, osteoarthritis, osteoporosis, periodontal diseases, inflammatory bowel disease, psoriasis, multiple sclerosis, cardiac insufficiency, atherosclerosis, asthma, chronic obstructive pulmonary disease, age-related macular degeneration, and cancers, comprising the step of administering to the living body an amount of a compound of claim 1 which is effective for alleviation of said conditions.

29- A pharmaceutical composition comprising as active ingredient an effective amount of a compound as claimed in claim 1, alone or in combination with one or more pharmaceutically-acceptable excipients or carriers.

30- A pharmaceutical composition useful in the method of Claim 28 comprising as active ingredient an effective amount of a compound as claimed in claim 1, together with one or more pharmaceutically-acceptable excipients or carriers.

31- A pharmaceutical composition useful in the method of Claim 28 comprising as active ingredient an effective amount of a compound as claimed in claim 2, together with one or more pharmaceutically-acceptable excipients or carriers.

32- A pharmaceutical composition useful in the method of Claim 28 comprising as active ingredient an effective amount of a compound as claimed in claim 3, together with one or more pharmaceutically-acceptable excipients or carriers.

33- A pharmaceutical composition useful in the method of Claim 28 comprising as active ingredient an effective amount of a compound as claimed in claim 20, together with one or more pharmaceutically-acceptable excipients or carriers.

34- Use of a compound according to Claim 1, for the preparation of a medicinal product intended for treating a disease involving therapy by inhibition of type-13 matrix metalloproteases.

35- Use according to Claim 33, characterized in that the disease is arthritis, rheumatoid arthritis, osteoarthritis, osteoporosis, periodontal diseases, inflammatory bowel disease, psoriasis, multiple sclerosis, cardiac insufficiency, atherosclerosis, asthma, chronic obstructive pulmonary disease, age-related macular degeneration, and cancers.

36- Use according to Claim 34, characterized in that the disease is arthritis.

37- Use according to Claim 34, characterized in that the disease is osteoarthritis.

38- Use according to Claim 34, characterized in that the disease is rheumatoid arthritis.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 01/11824

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D239/96 C07D487/04 A61K31/51 A61P19/02 C07D471/04
//(C07D471/04,239:00,221:00),(C07D487/04,249:00,239:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 818 819 A (E. C. TAYLOR, G. S. K. WONG) 4 April 1989 (1989-04-04) claim 9 ---	1-19
X	US 4 902 796 A (E. C. TAYLOR, G. S. K. WONG) 20 February 1990 (1990-02-20) claim 1 ---	1-19
X	US 5 646 141 A (M. D. VARNEY, W. H. ROMINES) 8 July 1997 (1997-07-08) * Compounds of formula V * --- -/--	1-38

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 March 2002	02/04/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Herz, C

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 01/11824

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	PATENT ABSTRACTS OF JAPAN vol. 12, no. 1998, 31 October 1998 (1998-10-31) & JP 10 195063 A (DAIICHI SEIYAKU CO., LTD.), 28 July 1998 (1998-07-28) * Compounds of formula I * abstract	1-38
A	WO 00 44716 A (AMERICAN CYANAMID CO.) 3 August 2000 (2000-08-03) claims 1-16	1-38
X	E. C. TAYLOR, P. S. RAY: "Pteridines. 51. A New and Unequivocal Route to C-6 Carbon-Substituted Pterins and Pteridines" J. ORG. CHEM., vol. 52, no. 18, 4 September 1987 (1987-09-04), pages 3997-4000, XP001062678 * Scheme I *	1-19
X	E. C. TAYLOR, G. S. K. WONG: "Convergent and Efficient Palladium-Effected Synthesis of 5,10-Dideaza-5,6,7,8-tetrahydrofolic Acid (DDATHF)" J. ORG. CHEM., vol. 54, no. 16, 21 July 1989 (1989-07-21), pages 3618-3624, XP001062654 * Compounds 14 & 15 *	1-19

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 01/11824

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